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HUGH THURSFIELD, D.M., F.R.C.P., and REGINALD MILLER, M.D., F.R.C.P.

WITH THE HELP OF

H. C. CAMERON, M.D., F.R.C.P.
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LEONARD FINDLAY, D.Sc., M.D.
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C. MAX PAGE, D.S.O., M.B., F.R.C.S.
LEONARD G. PARSONS, M.D., F.R.C.P.
G. F. STILL, M.D., F.R.C.P.
EDITOR OF THE *British Medical Journal*.

Vol. 5. JUNE, 1930. No. 27.

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ISSUED BY THE BRITISH MEDICAL ASSOCIATION.

London: British Medical Association House,
Tavistock Square, W.C.1.

Yearly Subscription (6 numbers), 25/- *Single Number, 4/6*

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OCCLUSION OF THE HEPATIC VEINS WITH CIRRHOSIS OF THE LIVER

BY

ROBERT HUTCHISON, M.D., F.R.C.P.,

Physician to the London Hospital, and to the Hospital for Sick Children, Great Ormond Street,

and

S. LEVY SIMPSON, M.D., M.R.C.P.,

Medical First Assistant, London Hospital.

The case described below is of interest, not only because of its rarity, but also because the patient had been observed over a large number of years. Primary carcinoma of the liver finally supervened, and the absence of ascites throughout the illness was also an unusual feature. The autopsy findings, and the pathological fact that occlusion of the hepatic veins rarely if ever occurs in a non-syphilitic cirrhosis, have led us to present the case as one of primary occlusion of the hepatic veins, with secondary fibrosis of the liver.

Clinical report.

The clinical records of this case extend over the years 1906 to 1929.

The patient, Herbert B., first came under observation in the year 1906, being then 5 years of age. He was one of a large family, and there was no clinical reason to suspect a syphilitic taint, but of course these were the pre-Wassermann days. The abdomen was said to have been very protuberant since he was a year old, and when first seen the liver was enlarged down to the umbilicus, and smooth and firm to palpation. The spleen at that time was not felt. There was no jaundice nor ascites, and though not a robust boy he presented no other signs of disease. No diagnosis was arrived at.

Two years later (1907) the notes show that the liver was ' becoming irregular ' and in the following year it is stated that ' the edge of the liver is now two finger-breadths above the umbilicus and the spleen can be felt one finger-breadth below the costal margin.' By 1910 the condition was unchanged and in 1912, the patient being then 11 years old, it was noted that ' the liver is the same and the spleen can just be felt.' His general health continued fair. There is no note of his condition after this until 1920, when the liver was only about one finger-breadth below the ribs and was ' rather firm ' ; the spleen could not be felt.

He was then lost sight of till September, 1929. He had now reached the age of 28 and complained of severe attacks of epigastric pain which had recently begun to trouble him along with some decline in his general health. Examination showed him to be a man of rather poor physique, thin and pallid, but with none of the ' cirrhotic facies,' no icterus, nor clubbing of the fingers. There were no stigmata of congenital syphilis. The liver could be felt about two finger-breadths below the edge of the ribs, it was hard and irregular, and apparently projecting from it in the epigastrium one could easily make out three rounded masses each about the size of a walnut. There was no ascites and the spleen could not be felt. The Wassermann test was negative and his other organs normal.

At the end of September, 1929, the abdomen was explored by Mr. A. J. Walton at the London Hospital who has kindly supplied the following note :—

'A considerable amount of clear serous fluid was found in the abdomen. The liver was somewhat enlarged generally with a coarsely irregular surface on which were several dilated veins, especially in the region of the falciform ligament. The liver substance was uniformly hard. Lying between the lower border of the liver and the transverse colon were three large rounded masses more or less sharply defined but involving the omentum, which was turned up over the colon. The liver, these masses, and the colon formed an arch under the tunnel of which the stomach and duodenum ran. The great omentum was divided from the transverse colon, which was allowed to drop into its place. The three masses (which were extremely vascular, were each about 2 in. in diameter and formed of friable material), could now be lifted up. The stomach and duodenum were quite free from the growths, which were firmly adherent to and originated from the free edge of the liver above. No secondaries could be found elsewhere in the peritoneum. The rest of the liver seemed to be free ; all the nodules in this organ appearing to the naked eye to be due to the cirrhosis and not to growth. The spleen was of normal size, although slightly firmer than normal. The area of attachment of the masses to the free edge of the liver was about 2 in. The liver was firmly held on either side and a wedge, to which the masses were attached, was excised much in the way that a slice of cake is removed. The two cut edges of the liver were then sutured together with thick catgut. There was no difficulty whatever in this owing to the firmness of the liver substance. One of the rounded masses was cut into and was found to consist of very soft friable material, almost certainly carcinomatous.'

The patient died four days after operation.

Pathological report.

Professor Turnbull has kindly provided the following report on the post-mortem examination made on this case.

Summary of necropsy.—General sero-fibrinous peritonitis. Operation: laparotomy and excision of primary carcinoma of liver. Typical and atypical, adenomatous and carcinomatous, regeneration of liver. Reticular fibrosis of liver. Anastomosis through capsule between hepatic veins within liver and veins of diaphragm. Occlusion of ostia of hepatic veins opening into inferior vena cava.

Thick layers of fibrin, enclosing four ounces of sero-fibrinous exudate, upon upper surface of left lobe of liver and adjacent diaphragm ; fibrinous adhesions and a few drachms of pus throughout remainder of abdominal cavity. Sero-fibrinous pleurisy (2 oz.) over lower lobe of left lung. Enlargement and slight fibrosis of spleen. Œdema and parenchymatous degeneration of kidneys. Congestion and mucous catarrh of stomach. Great dilatation of duodenum (circumference=13 cm.) and upper jejunum (circumference=15 cm.). Acid digestion of lungs. Œdema and parenchymatous degeneration of myocardium. Œdema of brain. Slight atheroma of thoracic and abdominal aorta. Thymus partly adipose. Red hæmatogenous marrow in neck and upper 7 cm. of shaft of femur.

Weights.—Body =99 lb. 10 oz. (45·1 kgrm.); liver =4 lb. 5½ oz. (1970·3 grm.); heart =8 oz. (226·8 grm.); kidneys =10¾ oz. (304·7 grm.); spleen =7¾ oz. (219·7 grm.); brain =3 lb. 0¾ oz. (1382·0 grm.); suprarenal bodies, =17·1 grm.; pituitary, =0·5 grm.; thyroid, =15·9 grm.; thymus, =3·9 grm.; pancreas, =53·4 grm.; bodies of testes, =25·8 grm.

The length of the body was 5 ft. 4 in. (1·63 metre).

Macroscopical examination.—The liver was enlarged, and the outer surface coarsely nodular ; the nodules measured up to 2 cm. in diameter. The cut surface showed scattered, stellate areas (cores up to 0·5 cm. in diameter) of grey or pink fibrous tissue, from which radiated trabeculæ of similar fibrous tissue. Between these stouter trabeculæ a net of very delicate sunken, grey trabeculæ separated subangular and rounded areas of moist, brown parenchyma of from 2 to 5 mm. in diameter. A large wedge-shaped area, with its base (5 cm. from side to side) at the hilum and its apex (4 cm. from side to side) passing vertically down the anterior surface of the right lobe, and numerous small areas immediately beneath the capsule were sunken and showed pin-head nodules of parenchyma, each with a portal system in the centre, lying close together in a sunken ground of partly blood-red, partly grey fibrous tissue.

A nodule (0·4 cm. diam.) of firm yellow tissue raised the capsule on the anterior surface of the left lobe, and a similar nodule (0·2 cm. diam.) lay a little distance beneath it. Slightly above its centre the postero-lateral margin of the right lobe was occupied for 6 cm. by raised, pure white nodules. Section showed this to be the base of a wedge of firm, greyish white tissue, closely beset with opaque yellow areas of necrosis, which extended inwards like a wedge for 3·5 cm. Immediately beyond the apex a large portal vein was distended by similar white tissue.

Four centimetres to the left of the round ligament was a vertical, sutured incision 5 cm. long. On section the incision lay in the centre of an area, 6 cm. in width, of opaque yellow necrosis. The portion of tissue removed by this incision had been received previously from the operating theatre. It consisted of a nodule (6× 6× 5·5 cm.) in a portion of omentum adherent to a segment (7× 6·6× 5 cm.) of liver. Along the line of excision of the segment of liver was a zone, 2 cm. wide, of fibrotic, brown hepatic tissue similar to that of the liver at necropsy. Within the zone were two rounded areas of white tissue, 1 cm. and 0·6 cm. in diameter. The rest of the liver, beneath the serous surface, was occupied by a hard mass. This showed a large central area of sunken dense grey fibrous tissue. From this fibrous strands passed radially to cut the surrounding tissue into lobules about 2·5 cm. in diameter. These lobules were subdivided by more delicate fibrous strands. The lobules consisted of firm tissue which was either grass-green or pale creamy brown. A line of fibrous tissue separated this mass from the zone of brown hepatic tissue. The mass in the adherent omentum consisted of soft, friable white tissue divided by indistinct trabeculæ into round lobules of a diameter of 0·8 cm.

The hepatic veins in the substance of the liver were abnormally wide and thick. The hepatic portion of the inferior vena cava was slightly narrowed (3 cm. in circumference) at the upper border of the liver, a raised ridge (1 mm. high) crossing its anterior surface and forking on the left. In this ridge there were a few venous orifices too minute to admit a probe. Opposite the right extremity of the ridge a strand of fibrosis (0·5 cm. wide) extended into the substance of the liver for one centimetre to end against the apparently blind extremity of a dilated (lumen, 0·5× 0·3 cm.) hepatic vein. This vein after a short course gave off a descending branch and then passed, with no appreciable diminution of its lumen, to the junction of the middle and outer thirds of the superior surface of the right lobe, where it pierced the capsule and joined a group of large, wide (widest diameter, 1 cm.) veins on the lower and upper surfaces of the diaphragm. In the inferior vena cava, 1·3 cm. above the left extremity of the ridge, was a faint scar. Beneath this, with its base against the vein, was a triangular area (0·5× 0·5 cm.) of fibrosis in the substance of the liver. The apex met the apparently blind extremity of a dilated (0·4 cm.) hepatic vein. This vein after a short course gave off a descending branch, and then passed horizontally across the liver to the left border, where, piercing the capsule, it passed, now 1·2 cm. in diameter, to the dilated diaphragmatic veins.

From a group of three openings (widest 0·5× 0·1 cm.), 1·4 cm. above the right extremity of the ridge, one vein passed within Glisson's capsule to the front of the superior angle of the right lobe, and others passed into the diaphragmatic veins. Another orifice (1·3× 0·6 cm.) in the inferior vena cava, 1·3 cm. above the left extremity of the ridge, led into a wide vein (2 cm. in circumference) on the inferior surface of the left dome of the diaphragm.

No trace could be found of the ductus arteriosus. The portal veins, bile ducts and gall-bladder were normal.

Microscopical examination. LIVER.—Portions of tissue for both embedding in paraffin and cutting on the freezing microtome for Herxheimer's method were taken from six portions of the liver that were free from carcinoma and showed variations in pattern to the naked eye.

All portions showed a reticular, the so-called portal, fibrosis: a network of fibrous trabeculæ of various breadths enclosed pseudolobules of various sizes. Most of the trabeculæ consisted of dense collagenous tissue which contained stout elastic fibres and was free from infiltration with round cells. The large stellate areas of fibrosis were found most frequently beneath the capsule. In these and the broader trabeculæ many portal systems lay close together; between them was a closely meshed net of broad bands of stout collagenous and elastic fibres; most of the meshes contained blood spaces, others contained pseudobile canaliculi, or, rarely, hepatic cells showing fatty degeneration. The narrower trabeculæ contained and united

both portal systems and sublobular or larger hepatic veins. A portal vein filled with granulation tissue was found in a trabecula. Trabeculæ formed by fibrosis round hepatic veins most frequently formed the boundaries of the pseudolobules, whilst the portal systems more often lay free in the pseudolobules or projected as spurs from the boundaries. Trabeculæ containing hepatic veins also projected as spurs into the pseudolobules. In addition, particularly in a section from a sunken area in the left lobe, an early stage of granulation was seen within pseudolobules. About central and sublobular veins, and uniting central veins to one another and to sublobular veins, were areas in which a net of bands of delicate collagenous fibrils, without elastic fibrils, contained in its meshes engorged sinusoids and numerous mononuclear leucocytes, large lymphocytes, small lymphocytes and cells loaded with fat and lipochrome. Most of the fatty cells were macrophages; others were neutrophil leucocytes, and hepatic cells; the fatty hepatic cells were confined to the periphery of the areas. The fat was almost entirely isotropic.

The pseudolobules varied greatly in size. The smaller were bounded by venous trabeculæ and contained one or more portal systems. The larger contained both portal systems and hepatic veins. The amount of hepatic parenchyma within the pseudolobules was greatly in excess of the normal; the normal relation of the enclosed portal veins to the central or sublobular veins was much disturbed; the radial arrangement of the columns was lost, the columns tending to be arranged concentrically in rounded masses at the sides of portal systems. The walls of the central and sublobular veins were thickened. The hepatic cells round them were fatty, and the columns were narrow or were replaced by a few rounded, dissociated cells. This degeneration and loss of cells round the hepatic veins was associated with a thickening and multiplication of the interstitial collagenous fibrils.

The yellow nodule beneath the capsule of the left lobe was found to be a pseudolobule of atypical constitution. It contained three portal systems. Except at the right and left margins the hepatic cells were considerably larger than in other pseudolobules, and had much larger nuclei and a slightly more basophil cytoplasm. They frequently formed columns many cells thick, and occasionally enclosed a lumen. They were polygonal. The nuclei varied considerably in size and in depth of stain; very large nuclei, multiple nuclei and karyokinetic figures were numerous. In the periphery at the two spots mentioned above, the columns of abnormal cells were directly continuous with columns similar to those in ordinary pseudolobules. On one side these ordinary columns were narrowed and pressed together concentrically round the mass of abnormal cells.

Microscopic examination was made of four pieces of the portion of liver removed from the left lobe by operation and one piece of the white mass found in the right lobe at necropsy. The sections included the two isolated nodules seen in the portion of liver removed at necropsy. The green and white growth was separated from the fibrotic liver of ordinary appearance by a fibrous capsule. In most of this capsule elastic fibres were sparse and delicate; in places the capsule was of the same constitution as the fibro-elastic trabeculæ in the liver, or such trabeculæ were included within it. The growth was divided into lobules by trabeculæ, some of which resembled those in the fibrotic liver, while others were broader and contained only a few elastic fibrils. Within the trabeculæ and septa many portal veins were filled with vascularized granulation or fibrous tissue. Some of the lobules were much larger than the pseudolobules in the fibrotic liver. One large lobule consisted of polygonal cells packed in a mass within which were a few branching capillary clefts. The clefts were bounded by a collagenous membrane, and their lumen was usually wide. The cells were of the size of normal hepatic cells or slightly smaller; their nuclei were very constant in size and structure, and resembled those of normal hepatic cells; their cytoplasm was usually as vacuolated as that of hepatic cells filled with glycogen.

In the other lobules the cells varied greatly in size but most were much larger than normal liver cells. They were arranged between capillaries either in solid columns or as tubes. Luminal spaces also lay within solid columns. The number of capillaries varied in different places, but they usually formed a net which divided the cells into elongated oval columns from two to twelve cells wide, or into tubules. The cells in the periphery of the solid columns were cubical or columnar, and those in the centre were polygonal. The cells that formed the well of tubules or lined luminal spaces within solid columns were usually tall, columnar but sometimes cubical. The number of tubules and luminal spaces varied in different places. The cytoplasm of the

cells was more basophil than that of normal hepatic cells. It was usually granular and vesicular. Vesiculation was frequently very conspicuous. Many cells were loaded with doubly refractile lipoid, but this did not account for all the vesiculation. The nuclei varied greatly in size and depth of stain. They were usually large, and many were very large. Multiple nuclei and karyokinetic figures were numerous. Similar cells sometimes filled lymphatic capillaries in the septa. In the mass from the right lobe there were large areas of dissociation and necrosis of the cells, often accompanied by hæmorrhage. The tubular lumina contained coagulated albumin, bile-stained albumin or bile, and also, frequently, a few round, fatty cells. Occasionally the luminal spaces were very wide. Wide capillary spaces were also present.

Omentum.—In the omentum the growth was again lobulated, and the interlobular septa contained few or no elastic fibres. In general there were fewer capillaries, so that the cells were divided into larger masses. There were some very wide capillary lakes. Lumina were also fewer; they again contained a bile-stained exudate. Many cells were loaded with doubly refractile lipoid. There were a few areas of hæmorrhage and dissociation and necrosis of the cells.

Hepatic ostia.—Selected sections were stained from a series taken from both sides of a cut through the blind extremity of the large right hepatic vein and the fibrous band which united it to the vena cava. The hepatic vein had a very thick media of large muscle fibres embedded in dense collagenous tissue, a narrow adventitia of collagenous and elastic fibres, and an intima of small muscle fibres and numerous delicate elastic and collagenous fibrils. Towards the vena cava it communicated with a venous sinus, whose relatively narrow wall consisted of a continuation of the intima and of a narrow prolongation of the media and adventitia, represented only by elastic and collagen fibres containing very few small muscle cells. Several veins with similar walls communicated with this sinus, and one could be traced to the adventitia of the inferior vena cava. This vein was filled with vascularized fibrous tissue containing numerous stout elastic fibres. Many other veins in the sections were filled with similar canalized dense fibro-elastic tissue. Other veins were filled with a younger granulation tissue free from elastic, and others with recent thrombus. The large hepatic vein lay within a large area, and the sinus was bordered by a zone of dense fibro-elastic tissue containing pseudobile canaliculi and groups of hepatic cells; this tissue was part of a network of dense fibrosis similar to that in the rest of the liver.

The only vein traced into the lumen of the inferior vena cava was a relatively small one. The mouth of the funnel formed by the vena cava at the orifice was filled, and constricted, by a mass of vascularized dense collagenous and elastic tissue, whose fibres were orientated differently from those of the intima with which they merge. The vein opened through a canal in this plug.

Interpretation of changes. Origin of the cancer.—The structure of almost all the pseudolobules is characteristic of an ordinary, typical regeneration of hepatic columns. In the yellow subcapsular nodule the greater part of a pseudolobule is occupied by cells which are atypical in appearance, frequently form columns of more than a double row of cells, and occasionally surround a lumen. These cells appear to have arisen in situ, because the columns in which they lie merge into columns of ordinary appearance. The pseudolobule appears to be the site of an atypical regeneration. The mass of white growth in the right border of the liver is probably a cancerous metastasis from the mass in the left lobe. It is of wedge-shape, and a portal vein at the apex of the wedge is filled with growth. In structure it resembles closely the mass in the left lobe, but forms smaller lobules in a more abundant stroma and is more necrotic. The mass in the left lobe is undoubtedly cancerous because it has extended into the omentum. That the cancer arose primarily in the liver could be recognized with certainty even before the necropsy, because the cells in places form tubules containing bile pigment. In one large lobule the cells and their nuclei are very constant in size and structure, and resemble closely normal liver cells loaded with glycogen or with glycogen and fat. This lobule is atypical in that capillary spaces are scanty, but from the character of the cells it appears histologically to be adenomatous rather than carcinomatous. The other lobules are composed of liver cells so atypical that cancer would have been indicated histologically even if infiltration of lymphatics and of the omentum had not been found. There is no direct evidence that this adenomatous and cancerous growth arose by atypical regeneration in pseudolobules. The

growth is arranged in lobules which are similar to the pseudolobules. But the trabeculæ bounding these lobules are for the most part composed of a fibrous tissue which contains few or no elastic fibres. Most of the trabeculæ are evidently of much more recent formation than the trabeculæ bounding the pseudolobules, and represent an interstitial reaction to the cancer. In view, however, of the regeneration throughout the liver and the atypical regeneration in the subcapsular pseudolobule there can be no doubt that the cancer originated in regeneration.

The cancer in the omentum is slightly more atypical than in the liver, capillaries being more scanty and columnar structure being in consequence less definite. Bile pigment is, however, still formed by the cells.

NATURE OF THE FIBROSIS.—In all sections there is evidence of 'back-pressure atrophy,' that is to say, of fatty degeneration and necrosis of the hepatic cells round central and sublobular hepatic veins. The cells nearer the portal systems, and therefore nearer the oxygenated blood, are healthy. In some areas this degeneration and necrosis is conspicuous, and cellular infiltration and early fibrosis involve all the cells except those grouped round the portal systems. There is here an early fibrosis which is doubtless due to the interference with the circulation. But most of the fibrous trabeculæ forming the reticular fibrosis throughout the liver are much older: they consist of stout collagenous fibres and numerous stout elastic fibres, and are free from cellular infiltration. The larger stellate fibrotic areas from which trabeculæ radiate are of similar age. These fibrotic areas and the stoutest trabeculæ have been formed by complete necrosis and fibrosis of whole lobules. The other trabeculæ have been formed by necrosis and fibrosis round hepatic veins and by fibrous elongation of portal sheaths. The resulting fibrous reticulum is not definitely due to 'back pressure.' In a reserved section from another case of occlusion of the hepatic orifices which shows undoubted 'back pressure' fibrosis, the fibrous tissue forms a small meshed net with a portal system in the centre of each mesh. In this section, however, the fibrosis is younger than in the present case, and regeneration is less. The old fibrosis in the present case resembles that of an ordinary, so-called portal, fibrosis. Nevertheless it could undoubtedly have arisen in necrosis due to interference with the blood supply. It appears, however, to be impossible to exclude a fibrosis due to toxins. Toxins attack first the cells farthest from the portal systems, that is farthest from the oxygenated blood. The cells round the central veins first degenerate and die; the degeneration and death then extend from centre to centre of the lobules at the points farthest from the portal systems. Granulation tissue and, ultimately, dense fibrous tissue replace the necrosed areas; at the same time there is infiltration and fibroblastic proliferation in the portal systems; the undamaged hepatic cells round the portal systems undergo proliferative regeneration. The ultimate picture is that of a typical so-called portal fibrosis. This sequence of changes can be followed in trinitrotoluene poisoning (Turnbull), and in my opinion they have taken place in almost every form of so-called portal fibrosis. In as much as toxins destroy exactly the same portions of the liver as interference with the supply of oxygen does, it appears impossible to determine in this case whether the initial fibrosis was due to toxins or whether it was due to occlusion of the hepatic orifices. The recent fibrosis in the present case is certainly due to interference with the circulation, and this is perhaps in favour of a similar origin for the old.

NATURE OF OCCLUSION OF HEPATIC ORIFICES.—The serial sections examined failed to show the junction of the large right hepatic vein with the inferior vena cava. The sinus with which it was connected was evidently only an entering branch. Many veins in the sections are filled with old vascularized tissue. They have been occluded either by inflammation (endophlebitis) or organization of thrombus (thrombophlebitis). Endophlebitis of large veins is very rarely, if ever, found in fibrosis of the liver other than syphilitic. In syphilitic fibrosis endophlebitis and endarteritis are often conspicuous, and the distribution of the fibrosis depends essentially upon the distribution of the endophlebitis or endarteritis. This was not the case in this liver. Occlusion of veins was seldom recognizable in this liver except in the fibrous tissue about the carcinoma and close to the inferior vena cava; there was no endarteritis. Close to the obstructed orifices in the inferior vena cava stagnation of blood and thrombosis would be very likely to occur. The sections actually showed recent venous thrombosis and obstruction of veins by granulation tissue in this region in addition to the old sclerotic canalized occlusions. There can be little doubt that the old occlusion was, like the recent, due to organization of thrombi, that is, to thrombophlebitis.

Although the large hepatic vein was not traced to the inferior vena cava, one smaller vein was so traced. The mouth of the funnel formed by the wall of the vena cava at the orifice of this vein was filled by a vascularized plug of stout collagenous and elastic fibres ; the vein communicated with a canal which passed through this. This plug or bridge was similar to those described and figured by Thompson and Turnbull[13], and as in those cases found its only reasonable explanation in the organization of a thrombus. Recent bracket-like thrombi at orifices are described and illustrated in the same paper. In another orifice in the inferior vena cava in the present case was a plug of fibro-elastic tissue which projected into the lumen of the vena cava like a plug of cotton wool from a test-tube. Unfortunately this orifice and its connections could not be traced farther in the series stained. That it was a plug of organized thrombus cannot be doubted.

Such evidence as has been obtained points to the ostia of the hepatic veins having been occluded by organized thrombus a long time before death. It is not possible to distinguish between the ages of this organization and of the older fibrous trabeculæ in the liver : both have reached too late a stage. The relation of the fibrosis to the occlusion has already been discussed. It might be added here that if occlusion of the hepatic orifices is a complication of non-syphilitic fibrosis of the liver, it is a very exceptional complication (H.M.T.).

History of the condition.

The first case of occlusion of the hepatic veins was described by Budd[1] in 1857, but the condition was not established as a separate entity until the researches of Chiari[2] were published in 1899. This author reviewed seven cases that were described prior to his own, and concluded that in all of them the obliterating phlebitis of the larger hepatic veins was interpreted as evidence of a process of contiguity and as arising from inflammatory processes in the vicinity of the veins. Chiari, however, described three cases of primary obliterating phlebitis of the hepatic veins, all in adults, in which the stenosis or obliteration was due to a thickening of the intima and was quite independent of changes in the surrounding tissue. This primary occlusion was considered by Chiari to be a disease sui generis, and in acknowledgement of his work the disease is sometimes named after him. He comments on the significance of his cases as follows :—

These three cases of obliterating phlebitis of the hepatic veins have much in common. In all there was inflammation in the wall of the veins, which, with the exception of the first cases, affected exclusively the intima ; even in the first case the adventitia was affected to a very much less extent. The process therefore represented an endophlebitis. The phlebitis was localized in all three cases in the same manner, i.e., in the proximal end of the hepatic vein, although in the third case there was some peripheral extension. There was always a definite tendency to obliteration, and in many cases complete obliteration. In every case it was an entirely independent process, unconnected with changes in the surrounding parts, and was also not secondary to a preceding thrombosis. The results of this phlebitis obliterans shewed itself in all three cases in the same manner : namely, congestion hyperæmia, atrophy, and induration of the liver, with congestion of the portal veins and a resulting fatal ascites. The thrombus which was found in the hepatic veins in all three cases, as also the thrombosis of the portal vein in the second case, I consider to be secondary to the phlebitis of the hepatic veins and to be brought about by the disturbance of the circulation in these veins. Nevertheless the secondary thrombosis was certainly of very great importance as leading to a disturbance of the circulation which became so severe that compensation by collateral circulation became inadequate, and a high degree of ascites developed.

In accordance with what has been said I do not hesitate to say that this independent phlebitis obliterans of the main trunk of the hepatic vein is a disease sui generis. With regard to its ætiology I have already pointed out that the phlebitis probably arises on a syphilitic basis and consequently should belong to the same category of circulatory lesions as syphilitic endarteritis obliterans of the cerebral vessels. Naturally further observations are necessary to confirm this.

Without detracting from the value of Chiari's histological findings it must be admitted, as other writers have pointed out, that the evidence of syphilis in all his cases is slender and unconvincing.

Some thirty cases have been described since Chiari's classical description, but we must limit our observations to those that have features in common with our own.

Previously recorded cases in childhood.—We have been able to trace records of six cases occurring in childhood. Gee[3] (1871) was the first to describe such a case, the patient being a male child, 17 months old, with a three months' history. Lazarus-Barlow[4] (1899) recorded the case of a boy of 13 years of age, with the unusual complications of hæmatemesis and melæna. Penkert[5] (1902) described the condition in a male child, 22 months old, whose abdomen had been distended from birth. Theodore Fisher's[6] case (1902) was a girl of 3 years of age ; Fabris'[7] case (1905) a male of 16 years of age ; and Hess's[8] case (1905) a girl of 16 years of age. The usual indication of disease in these cases was a swelling of the abdomen, attributed to ascites. Details of these cases are given in Appendix A.

Cases in which carcinoma of the liver supervened.—In 1918 Nishikawa[9] gave an excellent description of ten cases of primary occlusion of the hepatic veins. No less than four of these developed carcinoma of the liver, which he regarded as secondary to the parenchymatous regeneration in peri-portal areas. The cells of the carcinoma arose from the liver cells. Such a malignant neoplastic process is of course well known as arising secondarily to compensatory proliferation of the liver cells in hepatic cirrhosis due to other causes. There may be more than one focus of malignant transformation. Rosenblatt[10] in 1867, and Eppinger[11] in 1876, also described cases of hepatic vein occlusion, cirrhosis of liver, and carcinoma, but we have been unable to secure an adequate description of Eppinger's case. Synopses of these cases are given in Appendix B.

Previous cases without ascites.—The absence of ascites in our case must be considered a very unusual feature. We have been able to trace only two others where ascites was absent, both described by Nishikawa. In one, Case 8 of his series, as in ours, carcinoma supervened and it has therefore been included in the previous section. The other (Case 3) was of interest in that there was great varicosity of the œsophageal veins and a fatal œsophageal hæmorrhage. A slight degree of ascites was found at autopsy but was not recognized during life. The majority of patients with occluded hepatic veins die from the recurrent ascites and œdema. Of the three cases without ascites (our own case and the two of Nishikawa), two died of carcinoma and one of hæmatemesis.

Nishikawa[5] (Case 3 of his series).—Male, aged 31. Five months before death the patient developed œdema of the lower limbs. A few weeks later he noticed dilatation of the veins of the abdomen, and a swelling in the epigastric region. He complained of general malaise and epigastric discomfort. After one month the dilated veins increased, and following this the œdema became less although it never quite disappeared. The liver was felt to be enlarged but there was no ascites. A few days before death the patient vomited 250 c.cm. of blood. A clinical diagnosis of obstruction of the inferior vena cava and hepatic veins was made. At autopsy the clinical diagnosis was confirmed, the inferior vena cava being obliterated for a distance of 1 cm. near the diaphragmatic opening, and both hepatic veins being similarly obliterated at the site of their entrance to the cava. There was extensive diaphragmatic collateral circulation, well developed abnormal accessory liver veins, and multiple ruptures of varicose œsophageal veins. The liver showed a high degree of ' congestion cirrhosis.' There was a slight amount of ascites which was thought to have occurred just before death. The fact that a fatal rupture of œsophageal veins occurred in the absence of clinically diagnosable ascites, was considered of great interest. Nishikawa points out that Sascer found that in 200 cases of cirrhosis of the liver only three died of œsophageal bleeding unaccompanied by ascites.

General clinical features of the disease.

Although usually occurring before the age of forty the disease may manifest itself at all ages, and is found in both sexes. The majority of the cases in early life were in males. The onset may be acute or insidious, and the duration from a few days to many years. The liver is generally enlarged to palpation and its surface may be nodular. In acute cases it may be very tender. Ascites is nearly always present and is often associated with œdema of the legs, which, however, rarely precedes the ascites. The œdema depends upon the extent of involvement of the inferior vena cava. Dilatation of the superficial veins over the upper abdomen and chest wall is an important diagnostic sign. Jaundice rarely occurs. Symptoms are often indefinite especially in the early stages. Stabbing pains in the right hypochondrium and vague dyspepsia, with or without vomiting, may be complained of. Acute cases have been mistaken for poisoning or intestinal obstruction. In cases followed over a number of years it is possible to trace definite stages in the development of the disease. Thus the first sign may be a large liver, at a later date dilated superficial veins appear, and finally ascites ; or the number and extent of the superficial venous anastomoses may increase at definite intervals ; or a transient ascites may precede the terminal one by some years. Such incidents are probably due to successive occlusion of hepatic veins, which are compensated for by further anastomoses or possibly by canalization of older organized thrombi.

Usually the ascites recurs in spite of repeated paracentesis, death following within a few months. Carcinoma of the liver, with or without metastases, hæmatemesis due to rupture of varicose œsophageal veins, coma from hepatic insufficiency, or some intercurrent affection may be the immediate cause of death.

Cirrhosis of the liver, tuberculous peritonitis and carcinomatosis are the conditions which chiefly simulate the disease.

Pathological results of hepatic vein obstruction.

1. **Collateral circulation.**—The degree of collateral circulation depends upon the amount of obstruction in the hepatic veins, or in the vena cava at or above the junction of the hepatic veins. If the collateral circulation is adequate there may be no signs of disease, or at least no ascites, but sooner or later in most cases it breaks down. The most important collateral circulation takes place through the diaphragmatic veins and the accessory liver veins. In all cases numerous dilated and tortuous veins form plexuses on both sides of the diaphragm, and are a very characteristic feature at autopsy. Superficial cutaneous plexuses are also present in many cases. Less important compensation is evidenced by varicosity of the œsophageal and hæmorrhoidal veins.

2. **Congestion and fibrosis of liver.**—A description of the liver in several cases has already been given, so that the following is but a brief summary:—The intralobular and sublobular veins are grossly distended. The nature of the occlusion of the hepatic veins varies and is discussed in the section on ætiology. The changes in the liver itself are not constant. In the central acinous zone the parenchymatous cells are usually atrophied and sometimes entirely disappear. In their place there is a proliferation of connective tissue. The fibrosis of the atrophied areas is considerably greater than that which is usually found in cases of chronic heart failure. The fibrosis may extend to the portal areas. The atrophy of the liver cells in the central zone is partly ascribed to lack of nutrition and partly to pressure of congestion. The liver cells in the peripheral acinous zones are in most cases intact and often hypertrophied. These cells show evidence of regeneration, which is sometimes slight but usually well marked. In a few cases the proliferation may become atypical and progress to carcinoma.

Aetiology.

(1). **Endophlebitis.**—The term endophlebitis is used to indicate a primary inflammation of the vein with or without secondary thrombosis. In discussing Chiari's cases it was pointed out that he interpreted the histological findings as indicating an endophlebitis and not a thrombophlebitis. 'In every case it was an entirely independent process unconnected with changes in the surrounding parts and also not secondary to a preceding thrombosis.' Even if syphilis can be accepted as a cause of the endophlebitis in any of Chiari's three cases, there has rarely been any evidence of syphilis in subsequent cases. Nishikawa, in reviewing the literature, states that 'syphilis is without doubt a causal component but that the development of this disease is by means of a primary endophlebitic process must be denied.'

A case of endophlebitis of particular interest was described by Ohno[12] in 1921. There the histological picture was thought clearly to indicate a primary endophlebitis. 'All the liver veins, from the largest to the smallest showed intimal thickenings. In the intima, media, and adventitia, one saw in places a few lymphocytes, round cells, and plasma cells. The thrombi (seen at the junctions of hepatic veins) were fresh and not organized (as in other published

cases). There was a general diffuse thickening of the intima. The walls of the veins were so thickened that the lumen appeared to be almost stenosed. Complete obliteration however could not be made out, and organized thrombi were not found anywhere. There was a well-marked diaphragmatic collateral circulation.'

Ohno[12] considered the histological picture to be one of diffuse chronic phlebitis and to furnish a sure proof of a primary phlebitic disease (endophlebitis). He suggested that it is only in such early cases that it is possible to differentiate thrombophlebitis and endophlebitis.

Hess[8] in 1905 describing the case of a girl of 16, in whom the autopsy was performed by Chiari, was of opinion that the histological examination indicated a chronic inflammation of the veins or primary endophlebitis. No blood pigment was found in the connecting tissue obliterating the lumen of the veins.

(2). **Thrombophlebitis.**—This term is used to indicate a primary thrombosis with secondary changes in the vein wall. In 1912 Thompson and Turnbull[13] described two cases and put forward important histological evidence in favour of this ætiology of hepatic vein occlusion. The character of the tissues, their great vascularity, the position and sharp demarcation of the lesions suggested thrombophlebitis. To explain the site of the thrombosis the authors pointed out that at the diaphragmatic openings of the inferior vena cava there must frequently be retardation or even reversal of the blood stream consequent upon increase of pressure within the thorax; the ostia of the hepatic veins where the two blood streams meet with that of the inferior vena are positions in which eddies are liable to occur. Sharply defined projections of the intima are interpreted as organization of thrombi which have been silted up at the junction of converging streams of blood. Thompson and Turnbull nevertheless add that: 'Although as indicated above the ostia of the hepatic veins into the inferior vena cava would appear to be sites peculiarly favourable to the formation of thrombi, yet routine examination in a very large number of autopsies has shewn that the occurrence of such thrombi is of extreme rarity.' The possible influence of infection is considered and it is pointed out that in two cases (those of Chiari[2]' and Craven Moore[16]) symptoms followed two months and three years after pregnancy.

Aschoff[14] in 1912 discussed the deposition of agglutinated red cells, leucocytes, bacteria, and fibrin, on the intima of veins at the sites of constriction or widening, or at the confluence of blood-streams. This offers a further explanation of the site of thrombosis.

In 1918, Nishikawa concluded from a histological examination of ten cases that thrombophlebitis is the essential lesion. He uses the term, however, somewhat comprehensively so as to include primary endophlebitis. After considering the possible initial influence of infections, toxins, etc., he states 'I use the expression thrombophlebitis with regard to the disease not in the strict sense, but only as an expression which has come into general use. It is meant to include thrombophlebitis properly so-called (secondary phlebitis) and phlebitic thrombosis (in which the thrombosis is secondary).'

(3). **Mechanical hypothesis.**—In 1900, Kretz[15] explained the occlusion of hepatic veins on mechanical grounds. He pointed out that if the liver veins were closed for some distance, the obliteration was always oldest at the junction and most recent peripherally. The site first affected is thus the meeting point of a lesser and greater stream of blood. The intra-abdominal pressure and the hepatic ligaments help to keep the liver in position, but nevertheless the liver is to some extent suspended by the junction of the hepatic veins with the vena cava. It is thus possible for stress and strain to result in mechanical damage to the intima. The exuberant scar tissue may result in occlusion of the ostia of the hepatic veins. Such factors as violent coughing, jumping, etc., may thus be responsible. Nishikawa[9] suggested that if Kretz's hypothesis were right, the condition would occur more frequently, and especially with cases of abdominal ptosis. Kretz himself, however, does not deny the additional influence of infection, toxins, or even increased coagualability of the blood in the hepatic veins.

(4). **Congenital hypotheses.**—Rosenblatt[10] in 1867 first suggested a congenital origin. He did not, however, mean a congenital malformation, but postulated a fœtal interstitial hepatitis as the primary condition with secoondary occlusion of the hepatic veins. In his case the inferior vena cava passed through the liver fissure without receiving any branches from the liver parenchyma, but its inner walls showed light ridges and depressions as it passed through the diaphragm.

In the case described by Gee already referred to, the hepatic veins ended abruptly just short of the vena cava, being cut off from it by a thin membrane only. The lining membrane of the cava was perfectly smooth and natural, but where the mouths of the hepatic veins should have been, there were shallow dimples, which had not at all the look of scars. In considering congenital malformation, Gee wrote 'The liver may have been originally malformed so that the hepatic veins never did enter the vena cava; the cirrhosis which was undoubtedly present to a small degree being due to chronic congestion, which was manifested at last by the dropsy.' Gee, however, was unable to explain the closure of the ductus venosus, or the dimples in the vena cava which might indicate where the mouths of the hepatic veins had apparently once been. He therefore suggests an alternative explanation of primary cirrhosis of liver with secondary occlusion of the hepatic veins.

Fisher[6] in 1902 described the case of a girl, aged 3, where the cirrhosis was only very slight in extent; and in the same year Penkert discussed the case of a 22 months old child where swelling of the abdomen had been present from birth. The umbilical vein remained patent although the ductus venosus was closed. Penkert did not consider the latter fact to exclude a congenital origin although he gave no valid reason for so thinking. He concluded that the clinical and histological picture strongly supported a congenital ætiology and stated that 'a congenital malformation in my case is undoubted.'

In 1902[16] Craven Moore suggested a congenital susceptibility to obliteration. 'With the cessation of the placental circulation the ductus venosus which opens into the vicinity of the terminal portion of the right hepatic vein

becomes obliterated. This tendency to obliteration may persist in the immediate neighbourhood and may be recalled into activity by some irritant which would ordinarily remain without morbid manifestations.' Rolleston[17] put forward a similar view in commenting on Hoover's cases in 1920 : ' There may be a very remarkable lesion, viz., cicatricial contracture of the orifices of the veins and this may occur extremely early in life as in the case recorded by the late Dr. Gee. Possibly it is due to an extension of the process of obliteration of the ductus venosus, comparable to the excessive process described by Bland-Sutton as occurring at the site of the duct of Meckel's diverticulum in connection with the small intestine.'

In 1905 Fabris[7] described the case of a 16 year old boy where ' there was a rare form of atresia of the large liver veins at their junction with the inferior vena cava, which apparently is of congenital origin resulting from abnormal development.'

In 1918 Nishikawa[9], although not favouring the hypothesis of congenital malformation, observed that rudimentary congenital valves in the inferior vena cava sometimes occur in these cases and may be a factor in producing thrombosis.

With several cases occurring in the earliest years of life it is very natural that a congenital origin should have been suspected. Against this is the fact that many cases have occurred in the thirties and forties and occasionally even later, but this objection could also be put forward in such conditions as cervical rib and congenital cystic kidney. Certainly in the case of occlusion of the hepatic veins we know that there is a well-marked compensatory diaphragmatic venous anastomosis, and it is only when this breaks down that signs and symptoms manifest themselves.

More fundamental objections to the suggestion of a congenital malformation have been raised by several investigators which have constituted a stumbling-block to its acceptance, but we do not believe that these objections can be sustained. The chief point brought forward against congenital malformation is the failure of the ductus venosus to remain patent in those cases where the liver veins are not connected with the inferior vena cava. Although on first consideration this appears to be a logical objection, it fails to consider the result should the ductus venosus persist. From a teleological point of view this would be disastrous, as the liver would thereby be cut out of the circulation. It is much more reasonable to expect a compensatory anastomosis on both sides of the diaphragm, thus conveying the blood from the liver by a somewhat tortuous course which avoids the points of obstruction. This is exactly what is found in all cases.

Another objection to the hypothesis of congenital malformation is the presence of dimples at a situation where the hepatic veins usually join the inferior vena cava. These are interpreted as proof of the fact that the hepatic veins did originally join the inferior vena cava, and that they have become discontinuous through subsequent organizing thrombosis or perhaps even as a result of cirrhosis. There is, however, another possible explanation which would support the congenital hypothesis. It may well be that the normal intra-uterine

process of obliterating many of the venæ revehentes has progressed too far, and has failed to leave patent the two hepatic veins at their junction with the cava. The presence of dimples cannot therefore be considered as contradicting the hypothesis of congenital malformation, and in support of this contention Professor W. Wright has kindly sent us the following explanatory note :—

The course of the vitelline veins to the sinus venosus becomes interrupted with the formation of the liver and in consequence we get venæ advehentes leading to the liver, large blood spaces in the liver termed sinusoids, and venæ revehentes taking the blood from the liver to the sinus venosus. Prior to entering the liver the vitelline veins of either side are connected by the transverse channels. A vessel, the ductus venosus, soon makes its appearance running from the most proximal of these channels to the venæ revehentes of the right side. This vessel increases to such an extent that the right venæ revehentes by comparison appear to be mere tributaries. Later the vessel is joined by the corresponding venæ revehentes of the left side, with the result that we have a single vessel opening into the sinus venosus and receiving the venæ revehentes, which now become known as the hepatic veins. Immediately after birth the portion of the ductus venosus caudal to the openings of the hepatic veins becomes obliterated, the portion remaining becoming the upper or terminal part of the inferior vena cava. With such vascular changes variations may easily occur and certain of the hepatic veins may either fail to acquire, or may lose their connection with, the inferior vena cava.

It has also been observed (Thompson and Turnbull[13]) that the coats of the veins at the site of the obstructions are fully developed. Although this does not support a congenital ætiology, it is not necessarily a fundamental objection to it.

A further positive consideration in favour of a congenital origin is the fact that the site of obstruction is the meeting point of three venous channels, the hepatic veins, inferior vena cava, and ductus venosus, the last of which itself becomes obliterated up to the junction. On embryological grounds, therefore, a congenital stricture at this point would by no means constitute an unexpected congenital malformation.

Conclusions.—It is possible that primary occlusion of the hepatic veins may have several causes ; on the other hand some of the hypotheses of ætiology are not incompatible with one another. In many autopsies there is histological evidence of the presence of thrombi at various stages of organization. This suggests that thrombi have been deposited at different intervals during life. These findings are in keeping with the clinical histories in several cases. Thus we have seen that the disease may go on for a considerable time and its course be punctuated by episodes which can only be explained by further obstruction to the hepatic circulation, e.g., the sudden appearance of dilated epigastric veins with further extension at a later date, transitory ascites, or sudden pain and enlargement of the liver. Whatever the initial cause of the condition it is reasonable to suppose, especially in view of post-mortem findings, that these exacerbations are due to superimposed thrombosis, and that a possible recovery from them depends upon the evolution of additional compensatory venous channels. As to the immediate cause of these successive thromboses, one can only guess at such factors as toxins, infections, and even mechanical causes as suggested by Kretz. In some cases pregnancy, influenza, and whooping cough, have been known to precede the appearance of symptoms, although it is obviously difficult to say that these were really causal factors.

The acceptance of the occurrence and repetition of thrombosis is perhaps more important than the question whether there is initial inflammation of the wall of the vein. Although in most cases it would appear that no chronic inflammation of the intima, has preceded the thrombosis, it is not an easy histological problem to decide whether toxins, or infections, have affected the intima immediately prior to the deposition of a thrombus. Even more must this be the case when the thrombus is partly or completely organized, and the intima is secondarily affected. It has been seen that Nishikawa after a very extensive experience of the disease decided to use the term 'thrombophlebitis' so as to include both primary thrombosis and primary inflammation of the vein. It must be admitted, however, that in some cases (Thompson and Turnbull[13]) all the histological evidence is in favour of an apparently primary thrombosis.

Whatever view is taken as to the immediate cause of the recurring thrombosis, it still remains to account for the site of the lesion. Thrombosis at the junction of the hepatic veins is a great rarity in post-mortem examinations, and in these cases therefore it is reasonable to assume some primary predisposing factor. We are inclined to accept a congenital malformation as a possible explanation, especially when death occurs in early childhood, or when manifestations can be traced back to that period of life. The stasis resulting from complete obliteration or narrowing of veins would constitute an important factor in favouring subsequent recurrent thrombosis.

Summary.

1. A case of occlusion of the hepatic veins with cirrhosis, which began in early childhood and terminated 23 years later in primary carcinoma of the liver, is described.

2. A full account of the appearances found after death is appended.

3. The history of the condition is given with a summary (a) of cases previously recorded in childhood, (b) of those in which carcinoma of the liver supervened and (c) of those which resembled the present case in having no ascites.

4. The general clinical features are outlined and the hypotheses of causation indicated and discussed.

We are greatly indebted to Professor H. M. Turnbull for the pathological report on our case, although he is naturally not responsible for the views we have put forward; and to Professor W. Wright for his valuable help with the embryological aspects.

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APPENDIX A.

Previously recorded cases in childhood.

GEE[3] (1871).—Male child, 17 months of age who had had no illness until 14 months old, when he seemed to have pain in his belly, and his whole body swelled. In 2 days the swelling disappeared from the rest of the body and settled in the abdomen. When 16 months old the abdomen was tapped and 12 oz. of greenish serum were let out. The next day 2 pints were drawn off, and 3 weeks later 2 pints more. Five days after this he died.

AUTOPSY.—Liver a little smaller than usual; dense, tough and with thick round edges. Slightly nodular surface. Thickened capsule. Section of liver showed nutmeg appearance. The liver was congested, indurated, and fatty. The hepatic veins ended abruptly just short of the vena cava, being cut off from it by a thin membrane only. The lining membrane of the cava was perfectly smooth and natural, but where the mouths of the hepatic veins should have been, there were shallow dimples which had not at all the look of scars. Many of the larger branches of the hepatic veins were filled by tough colourless adherent thrombi. Extensive anastomosis of veins on both surfaces of diaphragm. Ductus venosus closed. Spleen natural size and rather tough. There was no description of the microscopic changes.

LAZARUS-BARLOW[4] (1899).—Male, aged 13. Four months before death the abdomen began to swell, the patient became languid and dyspnœic, and hæmatemesis and melæna occurred. He was a thin, slightly jaundiced boy, with gross ascites, a plexus of distended veins over the abdomen and distended venules on the cheeks. The edge of the liver was felt 3 finger-breadths below the costal margin. With regard to the question of syphilis, the evidence available was (i) that the mother had no miscarriages up to this, the 3rd child, but four afterwards; (ii) the histological character of the hepatic fibrosis. No alcoholic history. Paracentesis was performed twice (12 pints on each occasion). The patient gradually sank after the second paracentesis.

AUTOPSY.—Localized suppurative peritonitis. The liver, which weighed 2 lb. 10 oz., was granular, and mottled on the surface. On the upper aspect posteriorly was a large mass of cicatricial tissue which extended 1½ in. into the depth of the organ and involved the hepatic vein. Numerous branches of the hepatic vein, both large and small, were occluded by partially adherent and decolorized thrombus. The cicatricial mass suggested a former gummatous condition, and its edges shaded off in the form of trabeculæ of fibrous tissue into the (macroscopically) normal substance of the liver. At the same time the branches of the portal vein served as centres of a fibrous tissue overgrowth throughout the organ, so that a section revealed macroscopically a mottled surface in which foci of what appeared to be normal liver substance were separated by irregular trabeculæ of fibrous tissue, which stretched in all directions. Here and there were seen sections of the occluded hepatic vein. Microscopically the liver, even in its apparently most nearly normal regions, showed the existence of a mixed fibrosis. The greater part was of the multi-lobular variety, but there was much of the intercellular type. None of the white masses in the liver was found to be gummatous.

PENKERT[5] (1902).—Male, 22 months old, bottle-fed. History of whooping cough in the summer of preceding year. When 18 months old he could walk, but soon went off his feet. Since birth his abdomen appeared to be distended, but this increased markedly a few weeks before admission. At the beginning of April, 1902, dyspnœa was noticed. On examination he appeared to be a well-nourished, well-developed child, but somewhat anæmic. The abdomen was distended, and the umbilicus prominent. On the right side of the abdomen the liver could be felt enlarged and with a sharp edge reaching to the level of the umbilicus. Ascites and œdema of the abdominal wall were present. Urine normal. April 10th, 3 litres of clear yellow fluid of specific gravity 1011, and containing a large quantity of albumin drawn off. Dilated veins formed a caput medusæ round the umbilicus. A few days later another 3 litres were withdrawn. April 30th.: gross œdema of legs. A tentative diagnosis of congenital syphilis was made. On May 1st the abdomen was opened and much fluid was found. Liver enlarged to level of umbilicus, soft, smooth, congested. The spleen moderately enlarged. The Talma operation for draining the ascites was performed. A small piece of liver was taken for section and showed some atrophy and pigmentation. Liver acini not clearly seen, peripheral fat infiltration, marked dilatation of central veins. Thickening of peripheral connective tissue. Much congestion. A further tentative diagnosis of congenital heart lesion was then made. The child died on 3rd May.

AUTOPSY.—The liver was greatly enlarged. It had a sharp edge and bluish red surface. It was intensely congested. The left edge was definitely granular. The liver was soft and the capsule not thickened. The whole picture was that of severe congestion with parenchymatous atrophy. The cut section (after squeezing out the blood) was so spongy as to give the appearance of a cavernous angioma. There were hardly any clearly preserved acini. There was thickening of the connective tissue round the portal veins in the left lobe. Microscopic section of the liver showed great congestion, the central veins being much dilated and filled with blood. Between these were atrophied liver cells and bile pigment. There was periportal connective tissue surrounded by atrophied liver cells and fatty infiltration. 'In the left lobe there is nothing more left of the acinous structure. Here we have the distinct picture of a cirrhosis.' The spleen was somewhat enlarged and congested and showed small distinct follicles.

Heart and kidneys were normal. The inferior vena cava was somewhat twisted. The hepatic veins were indistinct. The lumen was only large enough to permit the passage of a hair-like probe and in the right vein there was a thrombus. The venules were obliterated, or almost filled with fibrous clot. Below the obstruction the hepatic veins were greatly distended but the majority were closed by thrombi. The wall of the vena cava was thickened. The umbilical vein permitted a small bristle to pass through it. The ductus venosus was closed.

FISHER[6] (1902).—Girl, aged 3. Seven months before death patient had an attack of whooping cough. For three months there had been swelling of the abdomen. On examination, several dilated superficial veins were seen in the upper abdomen and chest. There was marked ascites. The liver was enlarged four finger-breadths below the costal margin. The condition was thought to be due to cirrhosis. There was no evidence of syphilis. Paracentesis (65 oz.) was followed by rapid reaccumulation of fluid.

AUTOPSY.—The hepatic veins were found to be blocked by thrombi in varying degrees of organization. Both hepatic veins, where they should have opened into the vena cava, were found to be completely occluded. A small fibroid nodule marked the site of entrance of one hepatic vein into the inferior vena cava and a small depression the size of a pin's head that of the other. The walls of the hepatic veins were thickened but Fisher thought this might have been secondary to the thrombosis. The cirrhosis of the liver was only slight in extent.

FABRIS[7] (1905).—Male, age 16. This case is described as one of a rare form of atresia of the large liver veins at their juncture with the inferior vena cava which apparently is of congenital origin, resulting from abnormal development. Thrombosis of the intra-hepatic veins ensued, and following this there were special structural changes of the liver quite different from the usual passive congestion. (This summary is taken from an extract as we were unable to obtain the original paper).

HESS[8] (1905).—Girl, age 16. Four years previously she had been in hospital, suffering from dyspnœa and abdominal distension. Ascites was present but after 6 months' treatment by repeated paracentesis and diuretics it disappeared entirely. She was discharged with the diagnosis of hypertrophic cirrhosis of the liver, and remained quite well for nearly four years. On October 1st, 1904, 6 weeks before death, she began to have abdominal pain, and within 3 days marked swelling of the abdomen and distension of the veins of the upper abdominal wall appeared. Ascites was present, the liver was palpable 2 cm. below the costal margin and the spleen 1 cm. below the ribs, dilated veins were present over the abdomen and chest; there was no œdema of the lower extremities.

AUTOPSY.—The patient died on November 13th and Professor Chiari performed the autopsy. No patent branches of the hepatic veins were apparent near the vena cava, but, instead, what seemed to be obliterated veins. The intra-hepatic portion of the vena cava was remarkable in that no ostia of the hepatic veins were visible on its inner surface. The ductus venosus was obliterated. Microscopically the obliterated hepatic veins could be traced into the parenchyma, in some segments for 2 to 3 cm., extending from the vena cava as firm gray bands, without a lumen. The vena cava in the posterior surface of the liver shewed four minute ostia, ranging from a pinpoint to a pinhead in size. The connective tissue obliterating the lumen of the veins shewed no pigment. The liver was of the cirrhotic granular type with characteristic atrophy and regeneration.

APPENDIX B.

Previously recorded cases in which carcinoma supervened.

ROSENBLATT[10] (1867).—Male, 27 years old, admitted to hospital June 12th, 1867. Was apparently well until 7 weeks before admission, when he noticed a gradual swelling of the abdomen, with occasional generalized abdominal pains. His appetite became poor but thirst was increased. There was no marked fever. There was a history of paracentesis abdominis before admission, but the abdomen continued to swell, and there was œdema of the scrotum and lower extremities. Latterly the patient suffered from dyspnœa. There was no history of alcohol. On admission there was considerable ascites and the size of the liver could not be ascertained. There was tortuosity of the superficial abdominal veins. No albuminuria. The diagnosis was malignant or tuberculous ascites, and after repeated tappings the patient died on July 16th.

AUTOPSY.—The peritoneum was full of nodules which on microscopic section shewed alveolar carcinoma. In the right lobe of the liver there was a carcinomatous nodule the size of a goose's egg, which had become adherent to the hepatic flexure of the colon. A few nodules were present in the liver capsule. The left lobe of the liver was connected to the stomach wall by connective tissue containing numerous blood vessels. The veins from the stomach appeared to join the internal mammary veins on the other side of the diaphragm. There were adhesions from the liver to the diaphragm. There was an unusual and abundant venous anastomosis below the diaphragm. The portal vein appeared normal. The inferior vena cava passed through the liver furrow without receiving any branches from the liver parenchyma. Its inner walls shewed light ridges and depressions as it passed through the diaphragm. There was a partial cirrhosis of the liver. No microscopic description.

NISHIKAWA[9] (1918). (Case 4 of his series).—Male aged 26. While at school patient was said to have had swelling of the epigastrium and great impairment of appetite. When 23 years old he suffered from gastro-intestinal disturbances, swollen abdomen, diarrhœa, and fever. Following this there developed a pleurisy of the right side from which he recovered in two months. At that time an enlargement of the spleen was observed. One year before his death there was pronounced œdema of the legs which disappeared after a few days. His abdomen gradually became swollen. The œdema of the legs recurred 9 months before death and persisted. When the patient entered hospital, the subcutaneous veins in the anterior abdominal wall were dilated, the thoraco-epigastric and median xiphoid veins being varicose. Abdominal paracentesis was performed eleven times. At autopsy obliteration of the hepatic veins and of the inferior

vena cava was found. The latter was completely stenosed directly above the entrance of the liver veins by an organizing thrombus. Old and adherent, as well as fresh, thrombi were present in numerous liver veins. The ostia of the latter were occluded by fibrous tissue. The liver surface was uneven, irregular, and coarsely granular. On the posterior surface of the right lobe there was a prominent round nodule, the size of a pea which on section was seen to be of a marrow-like consistency and yellow-white in colour. Microscopically this nodule was of cancerous nature, arising from the liver parenchyma. The rest of the liver shewed 'congestion induration' with increase of connective tissue round the hepatic and sublobular veins. The liver cells in the centre of the lobules were atrophied but those in the peripheral acinous zone were unaffected, often hypertrophied, and proliferating.

Nishikawa (Case 5 of series).—Female, aged 34. For 10 years she had noticed recurrent transitory attacks of œdema of the legs and abdominal distension. This was probably associated with enlargement of the liver, as from the first a diagnosis of hepatic disease was made. At 26 years of age, marked dilatation of the subcutaneous veins of the abdomen was observed. A note states that when she was 32 the liver was felt after paracentesis to extend 3 finger-breadths below the costal margin. The surface was rough and the edge firm. A clinical diagnosis of obstruction of the intra-hepatic portion of the inferior vena cava was made. In spite of repeated paracentesis the ascites and also the œdema of the legs persisted for 18 months, the patient dying in January, 1915.

Autopsy.—The hepatic veins were obliterated at their openings into the vena cava, and there was marked stenosis of the latter as it passed through the diaphragm. The hepatic veins were thickened, and in places filled with thrombi. The inferior vena cava was almost completely obliterated by a fibrous mass for 1½ cm. The liver was granular and nodulated, the left lobe being markedly atrophied. The largest nodule was the size of a fist and was situated in the middle of the right lobe. It was greyish yellow, soft, and degenerated. Microscopically, the liver shewed the characteristic picture of 'congestion induration.' There was atrophy of the central parenchyma with hypertrophy and knotty hyperplasia of the peripheral acinous zone. Nishikawa concluded that 'the patient died of the intercurrent affection, parenchymatous liver cancer, which, unlike the former case (Case 4) reached an enormous size and was widely metastasized intra-hepatically as well as in other organs. With regard to its genesis it is to be regarded as secondary to a cirrhotic regenerative process. Finally, it must be emphasized that the cancer nodules were not present in the direct neighbourhood of the site of obliteration and consequently stood in no causal relationship to the closing up process.'

Nishikawa (Case 8 of series).—Female, age 38. Eighteen months before death the patient accidentally discovered a painless tumour, the size of a pigeon's egg, in the right hypochondrium. This gradually increased in size. Two months before death she complained of epigastric pain and loss of appetite, and was thought to have carcinoma of the stomach. On examination in hospital the liver was palpable 3 finger-breadths above the umbilicus in the median line. The surface of the liver was granular and a tumour was palpable in the right lobe. The clinical diagnosis was carcinoma of the liver. There was no œdema or ascites.

Autopsy.—The hepatic veins were found to be obliterated at their entrance to the vena cava. The interior of the latter was thickened and the lumen occluded just below this point. Adhesive thrombi were present in the hepatic veins. The liver surface was grossly irregular and contained several carcinomatous nodules. The left lobe was much atrophied and on its posterior surface were two tumours the size of a goose's egg. In the middle of the anterior edge of the right lobe was another tumour the size of a child's head. Microscopically the liver showed typical congestion cirrhosis. Hyperplasia and regeneration were, however, much less marked than in Cases 4 and 5. Metastatic cancer nodules were present in both lungs. Nishikawa considered the cancer to be a parenchymatous liver cancer. In view of the well marked collateral circulation, the absence of ascites, and the moderate degree of cirrhosis, he concluded that the patient might have lived many years but for the intercurrent cancer.

Nishikawa (Case 10 in series).—Male, age 28. Patient had noticed dilatation of the superficial abdominal veins at the age of 15. At the age of 22, he suffered from dyspnœa, palpitation, and œdema of the legs after slight exertion. There was also some cyanosis of the lips. At 24 there was some dilatation of the superficial epigastric veins. Three months before

death he vomited one litre of brownish fluid (? blood, ? wine). Five days later he suffered from marked dyspnœa and palpitation. At that time he was pallid and wasted. The superficial veins of the chest, abdomen, and back were enlarged and tortuous. Œdema of the legs was present, and the abdomen greatly distended. After paracentesis, a hard nodular tender tumour was felt in the epigastrium. In the right mammary line the liver edge was felt under the costal margin on deep inspiration. The spleen was not palpable. Paracentesis was performed four times in one month. Nausea and vomiting occurred, and he gradually wasted and fell into a terminal coma

AUTOPSY.—There was complete obliteration of all the principal liver veins at the point where they join the inferior vena cava, and occlusion of the inferior vena cava below this. The latter was completely closed below the hepatic vein ostia. The intima was generally thickened and there was a valve-like formation which was considered congenital. The hepatic veins showed fibrous occlusion and recanalization. A proliferating warty mitral endocarditis complicated the post-mortem picture. The liver surface was coarsely nodular and irregular, and several greyish white tumour nodules up to the size of a hen's egg could be seen. Microscopic examination showed characteristic 'congestion cirrhosis,' with atrophy of the central acinous zone, and hypertrophy and regeneration of the peripheral liver parenchyma. An atypical proliferation was regarded as the precursor of the carcinomatous nodules in the liver. Metastases of the parenchymatous liver cancer were present in the gall bladder.

THE SIGNIFICANCE OF THE PROTEIN CONTENT OF THE CEREBRO-SPINAL FLUID

BY

F. T. GREY, M.A., M.B., Ch.M.
Pathologist, East London Hospital for Children.

It is the purpose of this communication to lay special stress on the value of protein determinations in the cerebro-spinal fluid both on account of the rapidity with which they can be done and the information they yield if properly interpreted. Two specimens should be provided so that there may be a second tube to work on while the first is left in the incubator undisturbed for the formation of coagulum.

Protein.—The examination of a large number of specimens of cerebro-spinal fluid has brought out the great diagnostic value of accurate protein determinations. A method is proposed whereby it is possible within a few minutes to decide whether a meningitis may be ruled out. The following simple and rapid method is sufficiently accurate for this purpose :

A series of 12 small tubes ($\frac{3}{8}$ in. bore) are set up containing from ·010 to ·100 mgrm. albumin in 1 c.cm. saline. To each tube ·1 c.cm. of 25 per cent. salicyl-sulphonic acid is added. The tubes are sealed off and act as opacity standards which keep well, for although the protein settles, shaking will restore the colloidal dispersion for more than the time required for the test. The opacity produced by adding ·1 c.cm. of salicyl-sulphonic acid to 1 c.cm. of cerebro-spinal fluid is read against the standards. Dilutions with measured volumes of saline will be made if necessary. The outfit may be obtained from Messrs. Baird and Tatlock.

The following table of 101 cases, in all of which protein and salt were measured and the cytology and bacteriology done, shews :—

(1) that all (55) cases showing less than 0·04 per cent. protein are normal ;

(2) that those lying between 0·050 per cent. and 0·15 per cent. are, without exception, cases of tuberculous meningitis (plus four at 0·040) ; and

(3) that those (9) lying between 0·30 per cent. and 0·72 per cent. are cases either of pneumococcal or meningococcal meningitis.

Search for tubercle bacilli.

Meanwhile another tube has been left undisturbed in the incubator. It is inspected at intervals, without agitation, and a coagulum, if one is going to form, may be expected at any time between 2 to 24 hours. I am indebted to the ingenuity of my assistant, Mr. Nathaniel Smith, for the following very valuable modification of Canti's method :

Pour the fluid carefully into a clean watch glass, avoiding agitation, when the coagulum will be seen to retain its cobweb form ; cut a piece of

Case No.	Protein	NaCl	Cells	Organisms
2982/27	20	720	—	—
106/28	20	720	—	—
1862/28	20	710	—	—
1889/28	20	720	—	—
3036/28	20	700	—	—
4135/28	20	720	—	—
4180/28	20	700	—	—
33/29	20	690	—	—
1183/29	20	710	—	—
1044/27	25	720	—	—
2227/27	25	690	—	—
2890/27	25	720	—	—
3542/27	25	680	—	—
3794/27	25	700	—	—
920/28	25	720	—	—
1185/28	25	710	—	—
1499/28	25	710	—	—
1941/28	25	710	—	—
3466/28	25	700	—	—
4003/28	25	690	—	—
4197/28	25	720	—	—
4284/28	25	690	—	—
4154/28	25	710	—	—
167/29	25	710	—	—
172/29	25	710	—	—
514/29	25	720	—	—
522/29	25	670	—	—
789/29	25	700	—	—
863/29	25	720	—	—
879/29	25	720	—	—
923/29	25	720	—	—
1002/29	25	720	—	—
1011/29	25	720	—	—
1031/29	25	720	—	—
1087/29	25	710	—	—
1182/29	25	700	—	—
2557/27	30	720	—	—
3109/27	30	720	—	—
3425/27	30	700	—	—
3892/27	30	680	—	—
2225/28	30	670	—	—
3280/28	30	690	—	—
3465/28	30	680	—	—
36/29	30	700	—	—
89/29	30	680	—	—
150/29	30	690	—	—
257/29	30	710	—	—
593/29	30	710	—	—
625/29	30	710	—	—
677/29	30	690	—	—
927/29	30	700	—	—
957/29	30	700	—	—

Case No.	Protein	NaCl	Cells	Organisms
979/29	30	690	—	—
3330/27	35	690	—	—
4312/28	35	650	L7	—
1217/29	35	670	—	—
3272/27	40	650	—	—
3310/27	40	700	—	—
522/28	40	700	—	—
1240/28	40	690	—	—
3660/28	40	710	—	—
203/29	40	720	L20	—
257/29	40	660	—	—
283/29	40	680	—	—
645/29	40	680	—	—
1057/29	40	640		Tubercle bacilli
1445/27	40	640		Tubercle bacilli
1064/27	40	640		Tubercle bacilli
3906/28	40	600	L180	Tubercle bacilli
3332/28	50	600	L250	Tubercle bacilli
1477/27	60			Tubercle bacilli
213/29	60	630	L250	Tubercle bacilli
957/29	60	640		Tubercle bacilli
1074/27	70	630	L100	Tubercle bacilli
1542/27	70	670		Tubercle bacilli
3083/28	70	660		Tubercle bacilli
3153/28	70	630	L100	Tubercle bacilli
2818/28	80	630	L150	Tubercle bacilli
3723/28	80	640		Tubercle bacilli
3912/28	80	630	L150	Tubercle bacilli
2775/28	90	630	L150	Tubercle bacilli
1086/29	90	610	L175	Tubercle bacilli
1101/29	90	610	L170	Tubercle bacilli
373/28	100	670		Tubercle bacilli
2778/28	100		L180	Tubercle bacilli
684/29	100	600	L150	Tubercle bacilli
1120/29	100	600		Tubercle bacilli
2228/27	120	620	L800	Tubercle bacilli
2238/28	120	600		Tubercle bacilli
701/29	150	620	L175	Tubercle bacilli
846/29	150	620	L200	Tubercle bacilli
4061/28	150	620	L150	Tubercle bacilli
830/29	300		Pus	Pneumococci
1261/29	300		Pus	Pneumococci
1077/27	350		Pus	Meningococci
99/29	350		Pus	Pneumococci
1304/29	350		Pus	Pneumococci
1062/27	480	620	Pus	Meningococci
1078/27	480	620	Pus	Meningococci
2718/28	500		Pus	Pneumococci
720/27	720	630	Pus	Meningococci

Note.—A dash means 'none found'; a blank space means 'not done.' L = Lymphocytes. Figures for protein and NaCl represent mgrm. per 100 c.cm.

cigarette paper the size of a slide and with the aid of a pair of forceps, held in the right hand, lay over the surface of the coagulum, to which it will adhere if gentle pressure is made by means of a platinum loop held in the left hand. Transfer to the slide and blot dry with bold straight strokes. Carefully disengage the cigarette paper, when it will be found that the coagulum has adhered to the slide in its undisturbed condition. Dry in the incubator for two minutes and then fix by passing three times through the flame. Stain in the ordinary way.

By this method, tubercle bacilli have not once been missed in the last three years in a case of tuberculous meningitis in this hospital.

Conclusions.

(1) The estimation of protein is by far the most valuable single investigation that can be done on the cerebro-spinal fluid.

(2) An important modification (due to Mr. N. Smith) of the usual method of search for tubercle bacilli is described.

HUMAN CONTAGION AND TUBERCULOUS INFECTION IN CHILDHOOD

BY

BERNARD SCHLESINGER, M.A., M.D., B.Ch., M.R.C.P.,

and

P. D'ARCY HART, M.A., M.B., B.Ch., M.R.C.P.

(From the Children's Department, Royal Northern Hospital, London.)

The relative importance of heredity and contagion in the production of non-bovine tuberculosis, both in children and adults, has long been a subject of discussion. While many have sought the solution of this problem by statistical examination of the records of cases of clinical tuberculosis, the influence of exposure on tuberculous infection*, as opposed to manifest disease, has been less frequently studied.

There are, however, indications in the earlier literature that the very high incidence of tuberculous infection, which mass investigations with tuberculin tests revealed in the apparently healthy children of the densely populated continental cities of twenty years ago, was largely attributable to contact with open tuberculosis in the home and its vicinity.

Earlier investigations.

As early as 1909, Mantoux and Lemaire reporting 16 per cent. of reactors to tuberculin in a series of apparently healthy Paris children aged 1—2, 51 per cent. among those 2—4 years old, and 66 per cent. in the age-group 4—7, described their clinical material as 'sortant d'un milieu essentiellement misérable et fortement tuberculisé.' These authors contrast their figures with the lower percentages obtained in a better quarter of Paris. Similar findings were recorded in Lille by Calmette, Grysez and Letulle (1911), who pointed out the extreme frequency of reactors among children in towns where familial contagion was most intense. Lille was an example of such a town, and the figures given by these workers for its general population were only slightly lower than those reported by Cohn (1910) about the same time in another European city (Posen), for children who were drawn exclusively from tuberculous homes. Pollak (1911) found positive von Pirquet reactions in 96 per cent. of a series of infants under two years of age, living in tuberculous surroundings in Vienna, but his material largely consisted of sick infants brought up for treatment.

If contagion in the home is potent in producing tuberculous infection in children, a higher incidence of infection, as shewn by the tuberculin reaction, would be anticipated in children who are home-contacts† of open tuberculosis than among those who hail from non-tuberculous

*The term 'infection' which appears repeatedly in this paper signifies that the individual has at some time been infected with the tubercle bacillus. This does not necessarily imply that any active focus of disease is present.

†The term 'home-contacts' is used throughout this paper to denote children who have cases of tuberculosis living in their homes. It does not include children who have been exposed, in their homes or elsewhere, to tuberculous relatives, etc., if the latter do not reside with them. The term 'tuberculous households' is used in the same sense, and 'non-contacts' and 'non-tuberculous households' in exactly the opposite sense.

households. Tuberculosis, however, was rife, and the working-class population congested in many large continental cities at the time of the earlier investigations, to such an extent that a child, even though a member of a non-tuberculous household, was brought into frequent contact with tuberculous adults,—relatives, friends and neighbours,—in its home or the vicinity. The result was that, excluding infants, the risk of exposure run by a working-class child, who came from a non-tuberculous home, was not much less than the risk incurred by a child who was living in contact with open tuberculosis. Under these conditions it might be expected that, so far as the poorer classes were concerned, the direct comparison of the frequency of tuberculin reactions among these two groups of children would have led to confusion rather than to advancement of knowledge. Although we have been unable to find any continental urban statistics of this nature published at this period, the first enquiry in a large American city provides a case in point. This was a careful investigation carried out by Fishberg (1914, 1915) on a series of destitute Jewish children under 15 years of age, living in a congested tenement area of New York. These children were divided into two groups: (1) those whose parents were tuberculous, and (2) those whose homes were free of tuberculosis. The results were as given in Table 1.

TABLE 1.

NEW YORK INVESTIGATION (FISHBERG, 1914, 1915): COMPARISON OF TUBERCULIN REACTIONS IN CHILDREN WHOSE PARENTS WERE TUBERCULOUS (GRP. 1) AND IN THOSE WHOSE HOMES WERE FREE OF TUBERCULOSIS (GRP. 2).

Age	Group 1	Group 2
1— 3	Positive reactions in 55 per cent.	Positive reactions in 33 per cent.
3— 5	,, ,, ,, 69 ,, ,,	,, ,, ,, 41 ,, ,,
5— 7	,, ,, ,, 65 ,, ,,	,, ,, ,, 50 ,, ,,
9—11	,, ,, ,, 71 ,, ,,	,, ,, ,, 69 ,, ,,
13—15	,, ,, ,, 76 ,, ,,	,, ,, ,, 76 ,, ,,
All ages	,, ,, ,, 67 ,, ,,	,, ,, ,, 53 ,, ,,

Fishberg, apparently believing that the slight disparity was due to a small difference in technique, was led to conclude that 'the difference between those who lived in a tuberculous milieu and those who had no contact with consumptives in their homes, is apparently insignificant.'

Here, at first sight, might appear to be evidence against the potency of home contagion in determining infection. But investigations in rural communities, together with subsequent work in cities give a different complexion to Fishberg's results. Jakob (1911), working in a rural district of Germany, found that practically all the children living in houses where there were cases of open tuberculosis, reacted to tuberculin, while in the other homes a much smaller percentage of reactors was discovered. Overland (1913) found that the majority of the reactors in the Norwegian villages which he investigated came from tuberculous homes. Slater (1924–25) studied the tuberculin reactions of a wealthy farming community in Minnesota. The proportion of children infected was extremely low, being only 10 per cent. for all cases under 16. When, however, his cases were divided into those who had lived in a house with an open case of tuberculosis (61 children) and those who did not give a history of exposure (529), a very marked difference in the percentage infected was revealed, 80 per cent. of the former reacting to tuberculin, as against 5 per cent. of the latter.

Slater's figures for home-contact children in a country district are comparable with those obtained by Fishberg in some of the poorest and most congested parts of New York. On the other hand, the frequency of tuberculin reactions in non-contact children is entirely different in the two areas. The probable explanation lies in the different opportunities for making contacts. The environmental conditions of Fishberg's clinical material were such that, except for infants,

the risk of exposure for children of the same age, whether of tuberculous or non-tuberculous households, was much about the same, and it is therefore not surprising that only a slight difference was obtained between the tuberculin reactions of the two groups. In rural districts, on the other hand, the chances of contact are relatively slight for those who have no cases of open tuberculosis in their homes, and consequently the effect of home contagion is manifested sharply by the marked disparity between the tuberculin reactions of home-contacts and of children from non-tuberculous households.

This disparity has been noted, though to a somewhat less degree, in the majority of recent urban figures. Recent investigations of the tuberculin reactions of children of the urban hospital class in Europe and America shew that the incidence of infection is much lower than that reported a quarter of a century ago in many continental cities. It is also less than that recorded more recently for children of the lowest social status, such as destitute orphans drawn from highly congested and unhygienic surroundings. This difference in incidence of infection which has accompanied the improvement of environmental conditions and the decline in the tuberculosis death rate, indicates a decreased risk of exposure. Affecting, as might be expected, the non-contact population to a greater extent than children of tuberculous households, it has allowed the influence of contagion in the home to manifest itself, even in cities, by a significant disparity in the tuberculin reactions of the two groups.

Recent investigations.

More recently, Manning and Knott (1915) tested 228 children under 16 in Seattle, a comparatively modern town where housing conditions were much better than in the poorer quarters of most large continental or American cities. 166 of these children were living in intimate contact with active adult cases of tuberculosis; the remaining 62 children had no history of exposure. The percentage of reactors in the first group was more than twice that found among the latter (51 per cent. as against 23 per cent.).

Bernard and Debré (1920) made some interesting observations in Paris with the von Pirquet reaction on infants aged 0—2, who had been separated from their tuberculous mothers and placed in a creche. Of 58 infants whose mothers had bacilli in their sputum, 40 (69 per cent.) were found to be infected, as shewn by a positive tuberculin reaction, while of 65 infants where bacilli had not been discovered in the mothers' sputum or where the parents were not tuberculous, only 8 reacted (12 per cent.). All the infants who had been in contact with open tuberculosis for more than six months before separation were infected, all but one of the non-reactors having been removed 1 week to 3 months after birth. On the other hand, many of the infected infants had been in contact for only a few months. The infected group was followed up in order to discover if there was any association between the duration of contact and the ultimate prognosis. 40 per cent. of the infected infants died of tuberculosis, usually in the month following separation, and even though apparently healthy at that time. The other 60 per cent. of the infected infants were well when examined 2 to 24 months after separation. The duration of contact in both the survivors and the fatal cases of the infected group was from 2 to 3 months. The authors draw the conclusion that a certain time is required for contact to produce infection, but that this almost invariably results if the duration is prolonged to about 6 months. But their further conclusion, that separation of an infant from its tuberculous mother, may, even if already infected, save its life, is not warranted by the evidence which they give in this paper, for 40 per cent. of them died, and there was nothing to show that their fate would have been better or worse had they been left with their parents. This work does, however, suggest that separation of a contact infant which is not yet infected, is, if carried out early enough, the best way of preventing infection and of avoiding the possible fatal issue of this infection.

In a later paper Bernard, Debré and Lelong (1925) report the results achieved by 'L'Œuvre du Placement Familial des Touts-Petits,' founded in Paris in 1920.† They compare the fate during the first four years of life of (a) 265 infants with negative tuberculin reactions, separated from their tuberculous parents either at birth or later; (b) 171 infants separated when already infected,* but 'rigorously selected' according to the circumstances of their exposure; and

†A more recent account of the working of this system is given by Bernard (1927).

*See Footnote, p. 191.

(c) 66 infected infants who remained with their tuberculous parents. The tuberculosis death rate of the first group was nil; none of them developed clinical tuberculosis or even a positive von Pirquet reaction while under observation. 17 of the 171 infants in the second group developed clinical tuberculosis which was fatal in 13 (7·5 per cent.), meningitis and pulmonary disease accounting for most of the deaths. 82 per cent. of the third group, the infected infants who were left with their tuberculous parents, are stated to have died of pulmonary or meningeal tuberculosis, the majority in the first year of life. The rationale of separation of infants of the poorer classes before tuberculous infection has occurred thus appears to have been established. The advantage of separating infants already infected seems less certain, as the 'rigorous selection' of the 171 infected children for segregation makes them hardly comparable with the 66 infected infants who remained with their tuberculous parents. Nevertheless, the contention of these writers that this is the proper course to take is supported by their statement that of 13 infected infants who had passed the 'rigorous test,' but whose segregation was refused by their parents, 8 perished. It is interesting to compare the figures of Bernard and his co-workers with those of Walquist and Myers (1925) who followed up 71 tuberculin-positive infants under 2 (21 under 1) who were attending the out-patient clinic of the Lymanhurst school for tuberculous children, Minneapolis, the majority having been brought up not because of symptoms but mainly because of exposure. 96 per cent. of these infants gave a history of exposure: 73 per cent. to tuberculous parents, 11 per cent. to tuberculous siblings, and 11 per cent. to several sources of contagion. A tuberculosis fatality rate of only 8 per cent. was recorded, which was no higher than that found by Bernard and his associates among infants who were segregated after infection. This suggests that under favourable conditions the outlook for infected infants remaining in contact with tuberculosis is far from hopeless.

Schram (1921–22) investigated the von Pirquet reactions of 300 children from tuberculous homes in a poor quarter of Oslo. He obtained positive reactions in as many as 53 % of 113 infants under 1 year of age, and found that by 8 years four-fifths were infected. The incidence of infection was higher for those whose parents had positive sputum than for those whose family contacts had negative or no sputum, or whose source of contagion was a lodger. The value of Schram's work is unfortunately seriously affected by the lack of normal controls, and by the omission of clear details as to the age of those contacts whom he found to be clinically tuberculous, for the inclusion of such cases would naturally tend to raise the proportion of tuberculin reactors. A similar want of controls occurs in a paper by Barchetti (1921), who reported 73 per cent. of tuberculin-positive reactors in a series of 51 infants of tuberculous mothers in Vienna. Roepke (1923) working in Mannheim, found that the percentage of children in tuberculous households who reacted to tuberculin was greater if the source of contagion was an advanced case than if in an early stage of the disease.

The observations of Lampson (1923) on the spread of tuberculous infection in families indicate that the incidence of infection varies with the type of the tuberculous infective agent, being higher if this is an open case than if latent or healed.

Falk (1923–24) examined 68 children under 13, whose parents had open tuberculosis: 91 per cent. gave reactions with tuberculin (6 out of 10 infants less than a year old), the percentage being 100 in the case of 20 children of fatal cases. Girls seemed more likely than boys to receive infection from tuberculous mothers.

Austrian (1924) reported the results of an investigation carried out from 1915 to 1920 at a tuberculosis dispensary in Baltimore. He found that actually fewer children aged 0—9 years who had been exposed to a known case of clinical tuberculosis reacted than those with no known exposure. The figures were 67 per cent. (241 cases) and 74 per cent. (65 cases) respectively. Drolet (1924–25) published the tuberculin reactions of 1234 children with a positive parental history of tuberculosis, and of 461 with a negative parental history. His cases were drawn from a tuberculosis dispensary in the East-side district of New York over the period 1912–1916. In the first group 48 per cent. of those under 5 years reacted, 69 per cent. of the children aged 5—9, and 78 per cent. of the age-group 10—14. The corresponding percentages for the children of non-tuberculous parents were very similar, being 47, 64 and 74. The findings of Austrian and Drolet might be construed as evidence against the importance of family contagion in determining infection. But their controls are open to the serious objection that they were apparently

all children attending a tuberculosis dispensary, to which they must have been sent because of symptoms suggesting tuberculosis to their parents, since none of them were home-contacts; whereas many, if not most, of the home-contact series had been brought up because of exposure alone. For this reason the non-contact controls would be expected to be infected to a greater extent than the general non-contact population. The statistics of Sill (1918) appear to support the validity of this objection, for they were obtained, only a few years after Drolet's investigation, among children from non-tuberculous families of the hospital class living in the same district of New York. A much lower percentage of infected children was recorded, his figures being 10 per cent. for the age-group 4—5, 16 per cent. for children aged 8—9, and 48 per cent. for those who were 10—13 years old.

Myers and Magiera (1925), working in Minneapolis, examined with the von Pirquet test 761 contacts aged 0—19 years, the majority of whom were brought up because of exposure, or for symptoms which had suggested tuberculosis to their parents. All but 12 were under 16 years of age. These were compared with 784 cases (all but 25 less than 16 years old) with no known exposure to tuberculosis. Reactions were obtained in 57 per cent. of the contact group and in 29 per cent. of the control group.

Opie and McPhedran (1926), in Philadelphia, made a careful study of the spread of infection among children exposed to a tuberculous parent or sibling, using the intracutaneous (Mantoux) test as an index of infection. As controls they used children of families in which there was no case of tuberculosis. The percentage of reactors among 272 children who were home-contacts of open tuberculosis (bacilli in sputum) rose from 80 per cent. in the age-group 0—5, to 100 per cent. at 20, while in 179 non-contact controls the percentage rose from 23 per cent. among those aged 0—5 to 100 per cent. at 20. The results are shewn graphically on Chart 1. Of 124 children, one or both of whose parents suffered from open tuberculosis, 11 were found to have manifest disease themselves. These workers noted that reactions were more frequent among children in contact with a tuberculous parent (86 per cent.) than when in contact with a brother or sister (65 per cent.). Children whose parents, brothers, or sisters, had tuberculosis without bacilli detected in the sputum shewed a frequency of positive tuberculin reactions no greater than that found among the non-contact controls (44 per cent.). They ascribed these differences to varying duration and intimacy of contact. In a similar manner Opie and McPhedran observed the frequency of latent pulmonary foci in both groups of children by radiological examination, and found that, as with tuberculin reactions, the proportion rose with age, but was higher in the home-contacts than in the controls. The same differences were noted with regard to contact with open and closed tuberculosis, except that the incidence of latent lesions among the latter was greater than among the non-contacts.

From this résumé of the literature it will be apparent that considerable caution must be exercised in interpreting the results of investigations on the influence of contagion in the home on tuberculous infection. In many instances the clinical material has largely consisted of children from tuberculous households, brought up for symptoms suggestive of, or in some cases actually proved to be, manifest tuberculosis, with the natural result that a very high percentage of reactors has been obtained. Suitable controls are essential. Not infrequently they have been omitted altogether. In some of the published series the non-contact controls were composed of children brought up on suspicion to a tuberculosis dispensary, while a large proportion of the contact cases had attended only because of exposure. This is an unfair comparison.

It is best, in order to avoid two variables, to exclude all cases of suspect or definite clinical tuberculosis both from the series of home-contact children and from the control series of non-contacts. In this manner the most accurate estimate of the potency of contagion in the home in producing infection, as opposed to manifest or clinical tuberculosis, will be obtained.

Present London investigation.

The present investigation comprises a study of 118 London children of the hospital class, who came from tuberculous households. They were aged 0—15 years, 94 being less than 11 years old. The majority were brought up to hospital on account of exposure, or for some non-tuberculous complaint. All suspect or definite cases of clinical tuberculosis were excluded. This series was compared with 513 clinically non-tuberculous children of the same class and district, but whose homes were free of tuberculosis. These non-contact controls were also aged 0—15 years (438 being under 11 years of age), and were tested over the same period (twelve months) in 1929, by the same observer.

Many of the home-contact cases were drawn from the contact clinic of the North Islington Tuberculosis Dispensary, under the charge of Dr. W. E. Snell. The remainder were patients under the care of one of us (B.S.) in the Children's Department of the Royal Northern Hospital and in the out-patient department of the Hospital for Sick Children, Great Ormond Street.* The controls were drawn from the latter two sources.

TABLE 2.

COMPARISON OF TUBERCULIN REACTIONS IN HOME-CONTACTS OF PULMONARY TUBERCULOSIS AND NON-CONTACT CONTROLS.

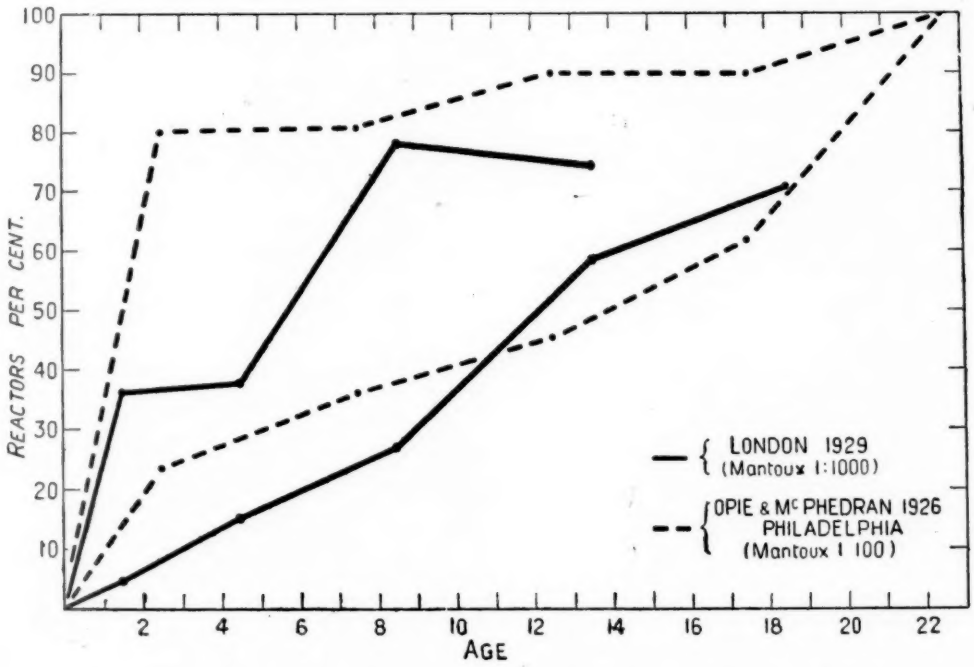
Age last birthday	Home-contacts of pulmonary tuberculosis			Non-contact controls		
	Number tested	Number positive	Percentage positive	Number tested	Number positive	Percentage positive
0—2	11	4	36	109	5	4·5
3—5	21	8	38	112	17	15
6—10	36	28	78	217	58	27
11—15	19	14	74	75	44	59
16—20	2	2	—	28	20	71
21—	14	13	93	118	106	90
0—10	68	40	59	438	80	18
0—15	87	54	62	513	124	24

The intracutaneous (Mantoux) test was used, and the reaction of each case to 0·1 c.cm. of 1/1000 dilution (0·1 mgrm.) of Old Tuberculin (Burroughs Wellcome & Co.) was ascertained. The tuberculin, of which the same batch was used throughout, was put at our disposal through the kindness of Dr. R. A. O'Brien, Director of the Wellcome Physiological Research Laboratories. It conformed to the Frankfurt standard, and in addition was standardized by the intracutaneous method on guinea-pigs.

*Part of this work was carried out while one of us (P. D'A.H.) held a Research Studentship at the Hospital for Sick Children, Great Ormond Street.

Of the 118 children under 16 years, 87 (68 under 11) were home-contacts of a relative who had pulmonary tuberculosis : in 50 of these cases (42 under 11) tubercle bacilli were present in the sputum ; in the remaining 37 cases (26 under 11) the sputum result was negative or not known. 31 children under 16 (26 under 11) were home-contacts of a relative who had non-pulmonary tuberculosis. The relatives with pulmonary tuberculosis were parents or siblings in all but four cases, where a grandparent (one case), uncle (one case), or aunt (two cases), was responsible. The relatives with non-pulmonary tuberculosis were parents or siblings, the latter predominating.

CHART I.



Tuberculin reaction of non-contacts and of home-contacts of pulmonary tuberculosis. The upper two curves are home-contacts ; the lower two curves are non-contacts.

The results of the pulmonary contacts in the different age-groups are compared with those of the non-contact controls of the same age in Table 2 and Chart I. It will be seen that, as with the curves of Opie and McPhedran, the incidence of infection increases from infancy to adolescence in both the home-contact and the non-contact series, but that the curve of the home-contacts runs above that of the non-contacts up to the age of 16. By 6 years of age half, and by 10 years three-quarters, of our home-contact series were infected, whereas only one-fifth and one-third of our non-contact controls were positive reactors at these respective ages. Similarly, by 5 years three-quarters of the home-contacts of Opie and McPhedran shewed positive reactions as compared with one-quarter of their non-contacts. In other words, most of the tuberculization of home-contacts takes place in infancy and early childhood,

i.e., in the home environment ; whereas at the present day most of the infection of non-contacts is received in middle and later childhood and in adolescence, i.e., during a period when the principal activities of the individual are away from the home. Both groups, however, are tuberculized to the same extent when adult life is reached. But the most striking difference is to be found in the shape of the two sets of curves. The home-contact curves obtained by Opie and McPhedran and ourselves rise rapidly at first, and then assume a more gradual slope ; the control curves, on the other hand, approximate to straight lines. This difference in shape is of some epidemiological interest. It indicates that the tuberculization of home-contacts has its maximum rate in infancy and early childhood, whereas the tuberculization of non-contacts occurs at approximately the same rate from birth to manhood. Such a dissimilarity is in keeping with a difference in the mode of contagion. Children in tuberculous households are subjected to contagion which is intense from birth, but children whose homes are free of open tuberculosis make their contact with the disease mainly outside the home, and with a frequency which increases as they grow up.

TABLE 3.

TUBERCULIN REACTIONS IN HOME-CONTACTS OF VARIOUS TYPES COMPARED WITH NON-CONTACT CONTROLS.

Group	No. tested aged 0—10	Number positive	Percentage positive
Home-contacts of pulmonary tuberculosis	68	40	59
Home-contacts of open pulmonary tuberculosis (bacilli in sputum)	42	29	69
Home-contacts of pulmonary tuberculosis where sputum result is negative or unknown	26	11	42
Home-contacts of non-pulmonary tuberculosis ...	26	4	15
Non-contact controls	438	80	18
Bedroom contacts of open pulmonary tuberculosis (bacilli in sputum)	34	24	71

Of the 68 children aged 0—10 years in our series, who were home-contacts of pulmonary tuberculosis, 59 per cent. reacted, as compared with 18 per cent. of 438 non-contacts of the same age (see also Table 3). These differences are more marked if the pulmonary home-contacts are divided into home-contacts of open pulmonary tuberculosis (bacilli in sputum), and home-contacts of pulmonary tuberculosis with negative or unknown sputum result. The percentages of children aged 0—10 in each of these groups, who were positive reactors, are compared with the non-contact controls of the same age in Table 3. It will be seen that positive reactions were obtained in 18 per cent. of the non-contact controls aged 0—10, in 42 per cent. of home-contacts of pulmonary tuberculosis with negative or unknown sputum result, and in as many as 69 per cent. of home-contacts of pulmonary tuberculosis with sputum known to contain

bacilli. This greater infectivity of open as compared with closed pulmonary tuberculosis is in agreement with the results of other workers already quoted.

The home-contacts of open pulmonary tuberculosis were next divided into those who had slept with the infective relative, and those who slept by themselves or with a non-tuberculous member of the family (Table 3). The percentage of tuberculin reactions among 34 bedroom contacts of open pulmonary tuberculosis, whose ages were 0—10, was found to be 71 per cent., a figure which is no higher than that of all the open pulmonary home-contacts together (69 per cent.). Since, however, four-fifths of the pulmonary home-contacts were bedroom contacts the statistical error of this comparison is considerable.

Comparison of the percentage of children infected when living with a parent, with that obtained when the tuberculous member of the household was a sibling, is not given, as the great preponderance of the parental contacts makes the figures of too little value.

In 26 children, aged 0—10, living with a relative (parent or sibling, the latter predominating) who had non-pulmonary tuberculosis, the percentage infected (15 per cent.), in marked contrast to the open pulmonary contacts, was no higher than in the non-contact group (438 cases, 18 per cent., see Table 3). While the numbers are small, they suggest that a positive family history of tuberculosis is only of importance in determining infection in so far as it yields a potential intimate source of contagion. If a familial inherited predisposition to infection existed, as many believe, we should expect this to be evident to some extent in children living in tuberculous families, no matter what the type of tuberculosis be. This point is of fundamental importance, and further work on a larger scale is required to decide it. If it can be shewn that children whose parents suffer, or have suffered, from non-pulmonary tuberculosis, have no higher incidence of infection, as shewn by their tuberculin reactions, than children with a negative parental history of tuberculosis, then the conception of inherited familial tendency to tubercular infection (in the sense already defined in this paper) will be rendered untenable.

In an attempt to throw further light on this problem, the non-contact controls were divided into those who had no tuberculous relatives, one tuberculous relative, and two or more tuberculous relatives. Each parent was carefully questioned on these points. The relatives include any of the following :—sibling, grandparent, uncle, aunt, great-uncle, great-aunt, great-grandparent, or first cousin—whether living or dead. It was not found practicable to classify according to the proximity of relationship. The comparisons are in any case crude, on account of the difficulty of eliciting family histories from hospital patients. The results for the children, aged 0—10, are given in Table 4. It will be seen that 22 per cent. of those with one tuberculous relative reacted,as compared with 15 per cent. who had no tuberculous relatives, while 46 per cent. of the children who had two or more tuberculous relatives gave reactions. While none of these relatives was living in the same house as the children tested (i.e., they were all non-contacts in the sense used through-

out this paper), many of them had pulmonary tuberculosis, and occasionally or frequently met the children concerned. These children, therefore, had a greater chance of becoming infected than children who had no tuberculous relatives, and who in consequence seldom met tuberculous adults. It will be noted that a smaller proportion of children with two or more tuberculous relatives, not living in the same house, were infected, than of children who had a relative with open pulmonary tuberculosis actually living with them (46 per cent. as against 69 per cent.). On the other hand, reactions were found no more frequently among home-contacts of non-pulmonary tuberculosis than among children who had no tuberculous relatives at all, the percentage being 15 in both cases.

The results which we have obtained for the infection incidence among pulmonary home-contacts are lower than those of many workers quoted (e.g., Pollak, Schram, Falk). This may be partly accounted for by the fact that we have excluded all suspect cases of clinical tuberculosis. By so doing we believe that we can obtain the best estimate of the influence of home contagion on the acquisition of tuberculous infection. It is also possible that the hygienic conditions in the homes of the children tested were better than in some investigations; this would tend to lower the infection incidence.

TABLE 4.

TUBERCULIN REACTIONS IN VARIOUS TYPES OF NON-CONTACT CONTROLS.

Children who are not home-contacts but have—	No. tested aged 0—10	Number positive	Percentage positive
2 or more tuberculous relatives*	35	16	46
1 tuberculous relative	50	11	22
No tuberculous relative	353	53	15
Total=non-contact controls	438	80	18

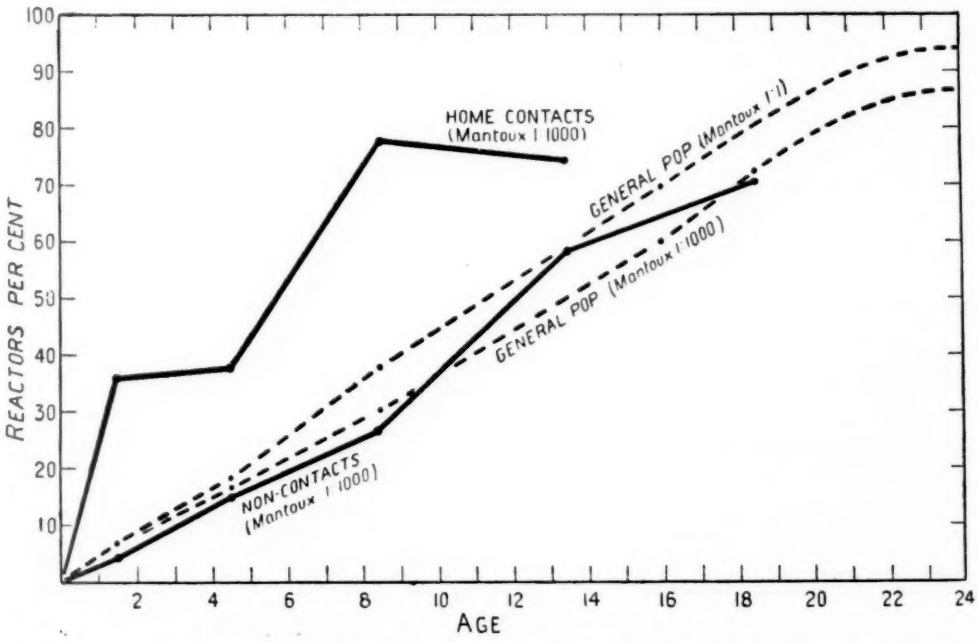
Our figures are open to at least two criticisms. In the first place the number of home-contact cases in each age-group is small, partly owing to the exclusion of clinically tubercular and suspect cases. This is admittedly true, but the statistical error is reduced by the adequate number of non-contact controls. The second possible objection is that while we have used the most delicate available test, the intracutaneous, we only give the figures for a dilution of 1/1000 tuberculin. Opie and McPhedran proceeded as far as a dilution of 1/100 before classing a patient as a non-reactor. The reactions in our control series are also given for a 1/1000 dilution. While this is the dose commonly accepted as standard by workers in this field, a significant percentage

*Sibling, grand-parent, uncle, aunt, great-uncle, great-aunt, great-grand-parent, first cousin—living or dead.

of additional reactors may be obtained, as Schroeder (1924) and one of us (Hart, 1930) have found, if stronger concentrations are used on cases negative to the standard dilution. If this occurred with the present control series more than with our home-contacts the differences which have been shewn between them would be less marked.

As a check, therefore, on our results the following procedure was adopted. The non-contact series which we have used as controls in this investigation does not form a true sample of the clinically non-tuberculous population, because the latter naturally contains some home-contacts. The non-contact controls were, in fact, obtained by extracting all the home-contacts from a series of 751 clinically non-tuberculous subjects of all ages, who formed a fair sample of the hospital class of north and central London in 1929. We have used this original series as a check on our results. The reactions to 0·1 c.cm

CHART II.



Tuberculin reactions of non-contacts and of home-contacts of pulmonary tuberculosis, compared with tuberculin reactions of general population (hospital class) of London, 1929. All clinically non-tubercular.

of a 1/1000 dilution of tuberculin was ascertained for all the 751 cases. A random sample of those who failed to react were tested with 0·1 c.cm. of a 1/100 dilution, and so on, with 1/10 dilution, and finally with 0·1 c.cm. of a 1/1 dilution (100 mgrm.). By this means the full sensitiveness of the intracutaneous method was brought into play, and by adjustment the reaction of all the 751 cases to a 0·1 c.cm. of a 1/1 (i.e., undiluted) tuberculin, which is the maximum intracutaneous dose, (100 mgrm.), was ascertained. The figures are not tabulated here, but those for 1/1000 dilution and for undiluted

tuberculin are plotted as curves and shewn on Chart II. The latter curve represents the maximum frequency of tuberculin reactions in the clinically non-tuberculous hospital class of London in 1929. Both curves, as expected, run above that of the non-contact series tested to 1/1000 dilution, but nevertheless both are much lower than the home-contact curve for 1/1000 dilution, shewing that the difference found between the latter group and non-contact cases is not a chance disparity nor due to insufficient dosage.

Discussion.

We are now in a position to discuss the relative significance of heredity and contagion in determining tuberculous infection, as opposed to tuberculous disease, i.e., clinical or manifest tuberculosis. This distinction is vital to the present issue. That the factors are not the same in the two cases is strikingly shewn by comparing the statistics of the mortality rate of tuberculosis with those of the incidence of tubercular infection. The incidence of infection in urban populations rises from birth to adult life, as shewn on Chart 2 for London. On the other hand, the mortality rate of tuberculosis is high in infancy, falls rapidly after 2 or 3 years of age, remaining low in middle childhood ; it rises again in adolescence to a high plateau in adult life (Registrar-General, 1927, 1928, 1929 ; Census of England and Wales, 1921). Thus in middle childhood, although infection is occurring as fast as at other ages, the mortality from tuberculosis is at its lowest.

It is believed by some that children with a strong family history of tuberculosis are more likely than other children to acquire tuberculous infection, because of an inherited predisposition, although contagion must finally determine this infection. According to those who hold this view, if two sets of children, one with a strong tuberculous ancestry, the other free of this taint, are exposed to the same infective agent, the former is more liable to become infected than the latter. There are several reasons for rejecting this view.

(1) The conception of familial diathesis is unnecessary. Children from tuberculous households have, as shewn in this paper, a much higher incidence of infection than those whose homes are free of tuberculosis, this being greater when the tuberculosis is active or open than when it is closed or healed. The severer the condition, the more likely is infection to take place. Children with a tuberculous parent or sibling living in their home are more frequently infected than those whose tuberculous relatives visit them occasionally ; the latter more frequently than those who have no tuberculous relatives at all. All these findings are satisfactorily explained by variations in frequency, intimacy and duration of contact, without having recourse to a belief in hereditary predisposition.

(2) The percentage of tuberculin reactions among children exposed in tuberculous households to parents, brothers or sisters with non-pulmonary tuberculosis appears to be no higher than among children of non-tuberculous

households; nor does it even exceed the frequency of tuberculin reactions found in those who have no tuberculous relatives at all. An inherited familial tendency to tuberculous infection should be evident, to some degree, in children living in tuberculous families, whatever the type of tuberculosis. But our figures (though the number of cases is small) suggest that a positive family history of tuberculosis is of importance in producing infection only in so far as it yields a potential intimate source of contagion in the shape of an open pulmonary case. Further work on a larger scale should decide this matter.

(3) Infants intimately exposed to a tuberculous individual who is not a member of the family rapidly acquire infection. Schloss, Holt and others have described this in the case of nurses. Schloss (1917) found that all but two of the infants in a ward where there was a nurse who had advanced tuberculosis, were infected, and gave positive tuberculin reactions. The two non-reactors were breast-fed by their mothers. In another ward where this nurse had only been temporarily, one-third of the infants were infected. Opie (1927) quotes Holt, who cites the case of ten infants infected within 14 months by a tuberculous midwife who used the mouth-to-mouth method of artificial respiration in the new-born.

(4) Infants separated from their tuberculous parents before infection has occurred, and placed in other families, appear to be no more liable to acquire infection in early life than infants of non-tuberculous parents.

We believe that the simplest view of the spread of infection in children of tuberculous families is as follows. Children with a strong family history of tuberculosis are more likely to become infected than other children, only because of the increased chance of contagion from an open case of pulmonary disease. This risk is naturally greatest if the patient lives in the children's home, and least when he only visits them occasionally. If the tuberculous relative has never seen the children, or is suffering from healed or non-pulmonary tuberculosis, they are, we suggest, no more likely than other children to become infected. We believe, further, that if two sets of children, one with a strong tuberculous ancestry, the other free of this taint, are exposed to the same infective agent, both are equally liable to acquire infection. Such a view is not inconsistent with a conception of heredity as a determinant of the subsequent course of this infection once it has taken place. The consideration of this matter, however, is beyond the scope of this communication.

Practical conclusions.

We believe that the facts presented in this paper, and the subsequent discussion, have a practical bearing on the prevention of tuberculosis, for they justify or suggest definite lines of action, some of which are already in force in this and other countries. It is clear that the system of allowing infants to remain with tuberculous parents, as practised in England, is the unnecessary cause of the loss of many lives. The recent careful study of the Lancashire Group of Tuberculosis Officers (1929) emphasizes this point. These

workers found that the tuberculosis death rate of 1,500 young children in tuberculous households in that county greatly exceeded that of the general population of Lancashire, which formed a control. The death rate from non-pulmonary tuberculosis (meningitis in two-thirds of the cases) among children living with an adult with positive sputum, was nine times greater in the age-group 0—1, fourteen times greater in the age-group 1—2, and nineteen times greater in the age-group 2—5. The actual tuberculosis death rate for children under 2 years of age in tuberculous households in which an adult relative had pulmonary tuberculosis (open or closed) was 1·7 per cent.; and 2·5 per cent. where the adult was the mother, and had a positive sputum. The substantial majority of these infants remained in contact with the tuberculous adult in their homes, except during the several months' institutional treatment undergone by some of the latter. Assuming, for the purpose of argument, that the figures which we have given for the frequency of tuberculin reactions among infants in tuberculous households, in which a relative has pulmonary tuberculosis (Table 2), to hold good for Lancashire, about a third of these infants, under two years of age, are infected. This would give a tuberculosis death rate of 5 per cent. to 8 per cent. for infected infants under two in tuberculous households of Lancashire, figures which are of the same order as that (8 per cent.) found by Walquist and Myers for contact infants under 2 years of age who were known to be infected. It is interesting to compare the fate of children in tuberculous families noted by the Lancashire Tuberculosis Officers with that reported for the Papworth Colony by Varrier-Jones (1927). He states that there has been 'a complete absence during 11 years of clinical tuberculosis in the 133 children of men and women who are definite cases of the disease and in most instances show tubercle bacilli in the sputum from time to time.' Whether the superior environmental and hygienic conditions of Papworth produce this result by diminishing the risk of massive and repeated infection, by influencing the course of the infection, or by preventing it altogether, it is impossible to decide without knowledge of the tuberculin reactions of the children in the colony. The researches of Bernard and his co-workers, already mentioned, suggest that each of these factors may play a part.

From Varrier-Jones' statement the Papworth system would appear to prevent the spread of tuberculosis in families. As an alternative, while prophylactic immunization (Calmette, 1928) is still on trial, the most effective preventive measure would be to separate infant from parent before infection has taken place. The Grancher system, when applied to uninfected infants for a period of several years, appears to be successful in France (Bernard, Debré and Lelong, 1925; Bernard, 1927). If infection has already occurred, as shewn by a positive tuberculin reaction, the value of separation is less certain, and it is possible that as much can be done by supervision at home. The present short period of separation during the institutional treatment of an adult is shewn from the Lancashire study to be totally inadequate.

Summary and conclusions.

1. Tuberculin reactions are more frequent among children of tuberculous households than among children whose homes are free of tuberculosis.

2. Children living with a tuberculous parent or sibling shew tuberculin reactions more frequently than children with tuberculous relatives who do not live with them ; and the latter more frequently than children with no tuberculous relatives.

3. A larger percentage of reactors is found among children who are living with a relative suffering from open tuberculosis than when the tuberculosis is closed.

4. These findings are adequately explained by variation in frequency, intimacy and duration of contact, without assuming the existence of inherited predisposition.

5. In a small series of children, living with a parent or sibling who had non-pulmonary tuberculosis, tuberculin reactions were no more frequent than among children of non-tuberculous households, and children with no tuberculous relatives at all. If further work, embracing a larger number of cases, confirms this finding, the view that children of tuberculous ancestry inherit a predisposition to tubercular infection will be rendered untenable.

We wish to record our thanks to Dr. W. E. Snell for his cooperation in regard to children from his contact clinic, and to Dr. R. A. O'Brien, Director of the Wellcome Physiological Research Laboratories, for placing the tuberculin at our disposal. To him, and to his colleagues, Dr. C. C. Okell, Dr. H. J. Parish, and Dr. J. W. Trevan, we are indebted for much valuable advice on the technical side.

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METABOLIC REACTIONS TO ACIDOSIS PRODUCED BY AMMONIUM CHLORIDE

BY

NOAH MORRIS, M.D., B.Sc.,

and

OLIVE MACRAE, M.B., Ch.B. (Faulds Fellow in Medicine, University of Glasgow.)

(From the Department of Pædiatrics, Glasgow University, and the Biochemical Department, Royal Hospital for Sick Children, Glasgow.)

Acidosis is so frequently put forward as the underlying pathological condition in such a variety of disorders that it is important to appreciate what actually are the metabolic manifestations of the acidotic state. Clinically one seldom if ever has an opportunity of studying acidosis uncomplicated by some such other factor as inanition or toxæmia. It is therefore advisable in an investigation of the metabolic reactions to a disturbance in acid-base equilibrium to have these secondary factors as far as possible excluded. This can only be done when the acidosis is induced in a healthy individual with the minimal amount of upset especially as regards food-intake, and such a condition is most nearly attained in the acidosis produced by the ingestion of ammonium chloride. Haldane[1] was the first to show that ammonium chloride taken in large amounts led to a marked acidosis owing to its ammonium moiety being converted to urea. Since then many papers have been published dealing with changes following the administration of this substance.

The present research was undertaken primarily with the object of studying the changes in mineral metabolism during acidosis and, if possible, of correlating these changes with other metabolic phenomena. Most workers are agreed that there is an increased output of lime in the urine during acidosis. The effect on the fæcal excretion of lime and the influence of the acidotic state on phosphorus metabolism have not, however, been clearly determined. Steenbock, Nelson and Hart[2] have pointed out the detrimental effect of acid-forming diets on calcium retention and calcification in animals. Sawyer, Bauman and Stevens[3] found an increased urinary output of calcium and phosphorus in two children during a period of high fat intake : in only one, however, was there an increase in the fæcal amounts of these substances, while in the other there was a decrease. In a study of acid and base-forming diets in adult women Bogert and Kirkpatrick[4] did not obtain a constant change in the amount of fæcal calcium during the period of acid-forming diet although the urinary lime was always increased.

In infants Flood[5] found that administration of N/10 HCl led to no alteration in the retention of calcium, although this substance always appeared in slightly increased amount in the urine. An accurate knowledge of the changes occurring in mineral metabolism during acidosis would, for instance, be invaluable in throwing further light on the pathogenesis and chemical pathology of such a condition as rickets. Freudenberg and Gyorgy[6] claim, indeed, that the fundamental factor in the hindrance of calcification in this disease is an increased acidity of the tissue fluids which prevents the precipitation of calcium salts.

It has been shown by Haldane[1], and Gamble, Ross and Tisdall[7] that salts such as calcium and ammonium chloride produce their diuretic effect in virtue of their acid-producing powers. This relationship between water-loss and acidosis has frequently been commented upon in states of dehydration accompanying gastro-enteritis. The opportunity was therefore taken in this study to attempt a correlation between the various metabolic changes following on the production of an acidosis by ammonium chloride administration. Gamble, Blackfan and Hamilton[8], and Følling[9] have shown the close relationship between the extra loss of water by the kidney and the excess excretion of fixed base. In this research it is hoped to bring forward evidence as to the part played by calcium and phosphorus.

Present investigations.

The subjects of the study were four apparently normal children—N.G., female aged 11 years ; W.C., male, aged 9 years ; N.M., female aged 10 years ; and J.F., male, aged 9¼ years. Each had recovered from a mild attack of rheumatism. The diet throughout the period of the investigation was constant, consisting of cow's milk with sugar sufficient to satisfy the caloric requirements of the child. After at least three days on the arranged diet the urine and fæces were collected with the usual precautions for periods of seven or six days as stated. Thereafter 1 grm. of ammonium chloride was administered 5 times daily in capsule form. The excreta were again collected for a period of 7 days. In the case of N.M. and J.F. the ammonium chloride was continued so as to include a third period of 5 and 6 days respectively. In the case of N.M. 1 drm. of cod-liver oil was given thrice daily during this last period.

The individual metabolic changes will first of all be discussed separately. Thereafter an attempt will be made to correlate the various findings with special reference to the defence of the organism against acidosis.

Clinical features.—No apparent change was produced in the appearance of any of the children during or following the ingestion of the ammonium chloride. In two cases the administration continued for a period of eighteen days without any sign of circulatory disturbance. The daily intake varied from 0·166 to 0·247 grm. per kgrm. of body weight. Haldane produced in himself marked respiratory distress by taking one dose of 25 grm. of ammonium chloride, equivalent to 0·25 grm. per kgrm. of body weight. Koehler[10] found that administration of 10–15 grm. of ammonium chloride daily to well-developed adults produced definite symptoms of listlessness, thirst, diuresis and muscular

aches : these subjects, however, were all patients recovering or recovered from lead-poisoning. Three explanations may be offered for the difference between our results and those recorded elsewhere. First, children may not be as susceptible as adults to the action of ammonium chloride. It is well known that children tolerate a much larger dose per kilogramme of body weight than adults of such a drug as salvarsan. It seems strange, however, that this should be the case with an acid-producing substance when the peculiar susceptibility of the young to disturbances of acid-base equilibrium is remembered. Secondly, the difference in the diets of our subjects and those of the adults may be of importance since milk contains an excess of fixed base over mineral acid. It is possible that this excess base enabled our subjects to withstand the acidosis more effectively than would otherwise have been the case. Thirdly, the division of the daily dose into five portions may have allowed the compensating reactions of the body to come into play before there was any necessity for visible extra effort on the part of the respiratory or other system. It seems to us that the last is the most likely explanation ; but whatever the cause may have been, the absence of clinical manifestations of acidosis in no way invalidates this study for, as we shall show later, the blood analyses were indicative of a disturbance of the acid-base equilibrium towards the acid side. Our principal object was to study the changes over a period of at least several days, and it would have been manifestly impossible to have accomplished this in the presence of respiratory distress or other evidence of acute acidosis.

Changes in chemical composition of the blood.—The changes in the chemical composition of the blood found during the ammonium chloride period are in close agreement with those reported by Haldane[1], and Gamble, Blackfan and Hamilton[8]. The changes in the individual constituents will be discussed in turn.

A. Carbon dioxide. (See Table 1, column 1.) The total CO_2 of the blood was reduced in every case. Keith and Whelan[11] found that the plasma CO_2 dropped about the 4th or 5th day of the administration of ammonium chloride. In the last three subjects the CO_2 content was estimated two or more times during the ammonium chloride period. From these results it is evident that the reduction in the CO_2 content reached what was practically its maximum, comparatively early in the reaction to ammonium chloride. Continued administration of the acid-producing substance had but little further effect on the CO_2 content of the blood. This is probably due to the fact that the other regulating mechanisms came into play, and thus protected the CO_2contents, and almost certainly the pH,from further reduction. Accordingly, if in any case the CO_2 content of the blood persistently falls from day to day,it would indicate that the other regulating reactions are unable to cope with the amount of acid produced.

B. Chlorine. (See Table 1, column 2.) The chlorine was moderately increased. The increase in chlorine when calculated in milli-equivalents of bicarbonate (Table 2) did not compensate for the decrease in milli-equivalents of bicarbonate. Baird, Douglas, Haldane and Priestley[12] found that the carbonate ion of the plasma and tissues is partly replaced by the chlorine ion in

TABLE 1.

CHANGES IN CHEMICAL COMPOSITION OF BLOOD.

Name	Stage	(1)	(2)	(3)	(4)	(5)	(6)
		CO_2 Vol. %	Cl′ mgrm. %	Fixed base c.cm. N/10%	N.P.N. mgrm. %	Calcium mgrm. %	Phosphorus mgrm. %
N.G.	Normal ...	55·1	300	158	36·5	—	—
	7 days NH_4Cl	38·7	350	154	46·1	—	—
W.C.	Normal ...	68·2	340	148	37	10·6	5·2
	4 days NH_4Cl	41·4	360	157	—	—	—
	8 „ „	40·3	340	157	44	10·1	6·5
J.F.	Normal ...	66·7	240	154	35·5	9·1	—
	9 „ „	49·1	360	159	48·5	9·1	—
	19 „ „	45·8	320	154	40·1	8·80	—
N.M.	Normal ...	60·6	285	147	35	9·25	4·2
	3 days NH_4Cl	45·1	290	—	—	—	—
	6 „ .	41·8	—	—	—	—	—
	9 „ „	43·4	280	132	46	9·8	4·1
	13 „ „	41·5	320	137	32	—	—

TABLE 2.

SHOWING COMPENSATORY DECREASE AND INCREASE OF CHLORINE AND BICARBONATE IONS RESPECTIVELY.

Name	Stage	HCO'_3 c.cm. N/10%	Cl′ c.cm. N/10%	HCO'_3+Cl′ c.cm. N/10%	Change of HCO'_3 & Cl′ from normal	Change in fixed base
N.G.	Normal ...	24·6	84·5	109·1	—	—
	7 days NH_4Cl	17·3	98·6	115·9	+6·8	—4
W.C.	Normal ...	30·4	95·7	126·1	—	—
	4 days NH_4Cl	18·5	101·4	119·9	— 6·2	+9
	8 „ „	18·0	95·7	113·7	—12·4	+9
J.F.	Normal ...	29·8	70.0	99·8	—	—
	9 days NH_4Cl	21·9	101·4	123·3	+23·5	+5
	19 „ „	20·4	90·1	110·5	+10·7	0
N.M.	Normal ...	27·1	80·3	107·4	—	—
	3 days NH_4Cl	20·1	81·7	101·8	—5·6	—
	9 „ „	19·4	80·3	99·7	—7·7	—15
	13 „ „	18·5	90·1	108·6	+1·2	—10

conditions of acidosis. Gamble, Blackfan and Hamilton[8] also reported similar results with both NH_4Cl and $CaCl_2$. In our cases, however, this replacement was by no means exact even when allowance was made for the change in fixed base. In W.C. there was an actual increase in fixed base accompanied by a deficit in the sum of bicarbonate and chloride. In J.F., on the other hand, the increase in chloride over-compensated the loss in bicarbonate: in this case the control period was characterized by a very low chlorine content. An objection may be raised that these analyses were performed on whole blood and not on plasma, but it should be remembered that the cell walls are equally permeable to chlorine and carbonic acid. It would seem, therefore, that all the acid ions take part in mutual compensation. As will be indicated later, there is but little change in the inorganic phosphorus of the blood. Indeed, the possible limits of the amounts of this substance and sulphate render a change in either almost negligible as a compensatory factor. It is probable that the organic acids of the blood play an important part in balancing excess or deficit of the other acids, as has been suggested by Gamble and his co-workers in alkalosis resulting from experimental obstruction of the pylorus. We have no data on the change in base-combining power of the plasma proteins, but the findings of Keith and Whelan[11], and Følling[9] suggest that such change is trifling.

C. Fixed base. (See Table 1, column 3.) Gamble, Blackfan and Hamilton[8] state that there is a very slight reduction in the fixed base of the serum, and Følling reports a fall of 15·4 milli-equivalents per litre. In two of our cases there was a decrease in the fixed base content of the serum: in one of these (N.M.) the reduction amounted to 15 milli-equivalents per litre, resulting in a value outside the normal limits. In the other two cases there was an increase in fixed base but the raised values fell within normal limits.

D. Calcium and phosphorus. (See Table 1, columns 5 and 6.) In 1924 Stewart and Haldane[13] noted a 10 per cent. rise in the serum calcium of a healthy adult, following the administration of 25 grm. NH_4Cl. Haldane, Wigglesworth and Woodrow[14] found no significant change in the inorganic phosphorus of the serum during acidosis but observed a slight fall as the acidosis was passing off. In the results recorded in Table 1, where the estimations were made after a variable period from the commencement of the acidosis, no constant change in either calcium or phosphorus was observed. In the other two subjects (Fig. 1 and 2) more frequent analyses were made. In both, the serum calcium showed an initial rise which persisted till the fifth day, thereafter falling below the normal level: on the cessation of ammonium chloride administration the calcium immediately rose somewhat above the 'control' level and then returned to normal. The serum phosphorus moved in the inverse direction to calcium.

E. Non-protein Nitrogen. (See Table 1, column 4.) In every case this was found to be increased. In the two cases in which it was determined twice during the administration of ammonium chloride, the value had fallen at the second estimation.

FIG. 1. CASE E. C. CHANGES IN CALCIUM AND PHOSPHORUS CONTENT OF SERUM.

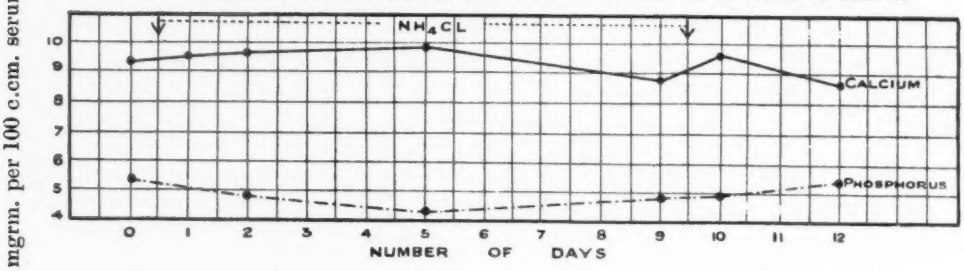
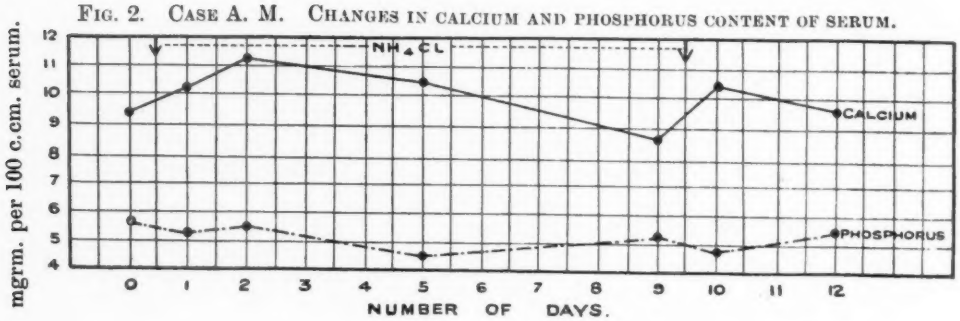


FIG. 2. CASE A. M. CHANGES IN CALCIUM AND PHOSPHORUS CONTENT OF SERUM.



Keith and Whelan[11] have shown that there is no increase in the ammonia content of the blood after ingestion of ammonium chloride. In our cases if the increase in non-protein nitrogen had been due to ammonia there would have been a rise in the ammonia value of from 8·5 to 15·8 mgrm. per cent.

TABLE 3.

BLOOD ANALYSES IN CASES OF CLINICAL ACIDOSIS.

Name	Condition	CO_2 Vol. %	N.P.N. Mgrm. %
J.H.	Acidosis; cyclical vomiting	36·5	60·0
	Recovered 2 days	48·8	40·0
H.P.	Gastro-enteritis	37·6	76·4
	Recovered	57·0	38·0
H.F.	Acidosis; ? gastro-enteritis	28·7	78·0
	Recovered	89·0	47·3
McP.	Acidosis; gastro-enteritis	26·8	52·1
E	Acidosis	36·1	109·1
E.F.	Gastro-enteritis	28·7	78·1
C.	Ileo-colitis	32·7	53·1
McG.	Gastro-enteritis	27·5	86·1

Such an amount of circulating ammonia would almost certainly have produced marked symptoms of poisoning, as ammonia is a very toxic substance. It is therefore highly improbable that the increase in non-protein nitrogen is due to ammonia nitrogen. A more reasonable explanation is that the rise is the result of increased breakdown of tissue proteins consequent on the disturbance of acid-base equilibrium. This view is supported by blood analyses in some cases of frank clinical acidosis (Table 3). It will be seen that in three cases during the stage of acidosis the non-protein nitrogen was increased, to fall to normal in the post-acidotic period. In cases of alkalosis where it also rises, the suggestion has been put forward that the cause is renal inefficiency. This can hardly have been the case in our subjects since, as will be seen later, there was a definite increase in the urinary output of ammonia, a good indication of unimpaired renal function.

Metabolism of calcium and phosphorus.—The intake and output of calcium and phosphorus in each case is detailed in Table 4 which also shows the retention and the partition of these substances between urine and fæces. In Table 5 are given the results of the fæcal analyses for calcium, phosphorus and fat.

It will be convenient to give a brief account of the results in each case, and thereafter to summarize and discuss the bearing of these findings on the general problem of mineral metabolism.

TABLE 4.

SHOWING INTAKE, FÆCAL AND URINARY OUTPUTS, AND RETENTION OF CALCIUM AND PHOSPHORUS (GRM.).

Name	Period		Total intake		Fæcal output		Urinary output		% of total output in urine		Total Retention		Retention per kgrm. per day	
	Intake	Days	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5
N.G.	Normal	7	20·16	27·72	9·508	6·818	1·406	11·55	12·8	62·8	9·246	9·352	·05	·05
	NH_4Cl	7	20·16	27·72	12·445	8·984	2·949	12·222	19·0	57·6	4·766	6·514	·025	·034
W.C.	Normal	7	20·16	27·72	14·983	14·390	1·521	9·464	9·2	39·7	3·66	3·87	·018	·019
	NH_4Cl	7	20·16	27·72	15·938	14·564	2·60	12·600	14·0	46·4	1·62	0·56	·008	·002
J.F.	Normal	6	13·44	18·48	8·621	7·494	0·683	7·686	7·3	50·6	4·136	3·30	·034	·027
	NH_4Cl	6	13·44	18·48	11·158	9·564	2·133	7·812	16·0	44·9	0·149	1·104	·001	·009
	NH_4Cl	6	13·44	18·48	8·823	7·728	2·099	7·392	19·0	48·9	2·518	3·36	·021	·028
N.M.	Normal	7	19·60	26·95	10·959	9·627	1·784	11·102	14·0	53·5	6·857	6·121	·033	·029
	NH_4Cl	7	19·60	26·95	19·649	17·445	3·192	11·928	13·7	40·7	—3·241	—2·759	—·015	—·013
	NH_4Cl & cod-liver oil	5	14·00	19·25	17·799	16·425	2·829	10·212	13·7	38·3	—6·608	—7·387	—·044	—·050

TABLE 5.

SHOWING ASH, CALCIUM, PHOSPHORUS AND FAT CONTENT OF FÆCES.

Name		Period 1 (normal)		Period 2 (NH_4Cl)	
		Total quantity in fæces grm.	% in fæces	Total quantity in fæces grm.	% in fæces
N.G.	Fæcal weight	62·55		66·55	
	Ash		31·8		36·2
	CaO	9·508	15·0	12·445	18·0
Weekly	P_2O_5	6·818	10·9	8·984	13·0
figures	Total fat	21·736	34·75	19·486	29·28
	Combined fatty acids	17·795	28·45	15·659	23·53
	Free fatty acids	1·189	1·9	1·637	2·46
	Neutral fat	2·752	4·4	2·189	3·29
W.C.	Fæcal weight	84·65		88·40	
	Ash		40·8		41·0
	CaO	14·983	15·0	15·938	18·0
Weekly	P_2O_5	14·390	14·0	14·564	14·0
figures	Total fat	29·527	33·7	24·699	27·94
	Combined fatty acids	17·437	20·6	14·003	15·84
	Free fatty acids	6·833	8·19	7·284	8·24
	Neutral fat	4·156	4·91	3·412	3·86

Name		Period 1 (normal)		2 (NH_4Cl)		3 (NH_4Cl)	
		Total quantity in fæces grms.	% in fæces	Total quantity in fæces grms.	% in fæces	Total quantity in fæces grms.	% in fæces
J.F.	Fæcal weight	56·35		79·70		60·85	
	Ash		33·2		31·5		32·8
	CaO	8·621	15·3	11·158	14·0	8·823	14·5
6-day	P_2O_5	7·494	13·3	9·564	12·0	7·728	12·7
figures	Total fat	20·70	36·79	33·386	41·89	20·00	32·92
	Combined fatty acids ...	14·01	24·95	18·18	22·81	12·64	20·81
	Free fatty acids	4·89	8·652	13·047	16·37	5·57	9·18
	Neutral fat	1·80	3·188	2·16	2·71	1·78	2·93
N.M.	Fæcal weight	8·65		13·69		18·05	
	Ash		40·8		44·7		43·4
	CaO	1·565	18·0	2·807	20·0	3·556	19·0
Daily	P_2O_5	1·375	16·0	2·492	18·0	3·285	18·0
figures	Total fat	2·85	33·03	3·936	28·75	6·58	36·4 5
	Combined fatty acids ...	2·204	25·48	2·909	21·25	5·008	27·75
	Free fatty acids	0·236	3·43	0·602	4·40	0·826	4·58
	Neutral fat	0·376	4·12	0·424	3·10	0·743	4·12

N.G. The retentions of CaO and P_2O_5 were reduced. The output of lime in the fæces was increased as the result of an increased percentage of CaO in the fæces and also a rise in the weight of the dried fæces. The urinary excretion of lime was also increased. The output of P_2O_5 by the urine was likewise raised, but the decreased retention of P_2O_5 was mainly the result of an increased fæcal content of this substance. As with lime the rise in fæcal phosphorus was consequent on an increased percentage output together with a rise in the fæcal weight. The percentage of ash was also increased, while the percentage and absolute amounts of total fat and combined fatty acids were decreased.

W.C. The results here were practically identical with those recorded above. One point of difference may be noticed, namely, the fact that there was but little increase in the fæcal output of P_2O_5, the lowering of the retention value being due to a fairly marked rise in the urinary content.

J.F. In this case there were two successive periods on NH_4Cl. The retentions of CaO and P_2O_5 were reduced during the first of the two periods but returned practically to normal in the second. There was a rise in the urinary CaO in both periods, and the urinary P_2O_5 in each was practically unchanged. The reduced retentions of lime and phosphorus were due entirely to the increased fæcal output resulting from a rise in the fæcal weight; the percentages of ash, calcium and phosphorus were all reduced. The percentage of total fat in the fæces was increased during the first period because of the marked increase in free fatty acids, while in the second period the value for total fat was slightly below that of the normal. The percentage of combined fatty acid was reduced during both periods.

N.M. With this subject there were two periods on NH_4Cl, the first for 7 days and the second for 5 days during which time one dram of cod-liver oil was given three times daily in addition. A negative balance of both lime and phosphorus was found during each NH_4Cl period, being much more marked on the second. The urinary output of lime and phosphorus was increased on both occasions, the increase in urinary phosphorus being much more marked in the second of the two periods. The percentages of lime phosphorus and ash in the fæces were increased, but the marked rise in the total fæcal output of CaO and P_2O_5 was chiefly the result of the striking increase in the weight of dried fæces. In the first period the percentages of total fat and combined fatty acids were reduced but in the second, during which cod-liver oil was also administered, these percentages were increased slightly above those outlined in the normal period.

SUMMARY.—There was in all cases a reduced retention of lime and phosphorus resulting from an increased output of these substances in both urine and fæces.

(a). Calcium.—Goto[15] found in acidosis an increased excretion of calcium by the urine but Keith and Whelan [11] observed but little change in the urinary excretion of calcium during administration of ammonium chloride. In our cases, however, the urinary calcium was at least doubled and in one instance trebled. The increased fæcal excretion of calcium was due to an increase in the total fæcal weight and, with the exception of J.F., an increase in the percentage of lime in the fæces. Generally the increase in fæcal calcium was much greater than that obtained in the urine. In W.C., however, the urinary and fæcal increases were approximately equal, and in J.F. (2nd period) the urinary increase exceeded that in the fæces.

(b). Phosphorus.—The extra output of phosphorus was even less consistently distributed between urine and fæces than was the extra lime. In only one case (W.C.) was the increase in urinary phosphorus marked. Apart from this case, in which the rise in fæcal phosphorus was insignificant, the main increase in excretion was by the fæces.

(c). Weight of dried fæces.—In all cases there occurred an increase.

(d). Ash.—With the exception of J.F. (1st period) there was always a rise in the percentage of ash in the dried fæces.

(e). Fæcal fat.—The percentage of total fat in the fæces was reduced in all cases except J.F. (1st period) and N.M. (2nd period). The percentage of combined fatty acids was reduced in all cases except N.M. (2nd period).

Discussion.—In spite of the large amount of work done in connection with calcium metabolism there is as yet no definite information as to the extent of absorption of this element, and it is still a matter for conjecture how much of the fæcal calcium has been absorbed and excreted through the bowel wall, and how much has passed through the gut unabsorbed. Grosser[16] found that subcutaneous injection of calcium salts led to an increased excretion by the bowel, and Salvesen[17] showed that in parathyroidectomized dogs, of calcium chloride injected intravenously, nine-tenths was excreted in the fæces and one-tenth in the urine. Percival and Stewart[18] isolated the large intestine in cats and found that the intravenous administration of calcium chloride was followed by a marked increase in the excretion of calcium by the large intestine, but no change in the urinary output. Recently Bauer, Allbright and Aub[19] have published the results of an investigation of the calcium metabolism on a very low calcium intake in 13 normal adults. On these 13 subjects there were 46 three-day periods of investigation. With the exception of a single period in one case, they found in all a negative balance of calcium, and with the exception of three periods there occurred in the fæces a greater amount of lime than had been ingested. In one case (N.M.) of our series during each of two periods on ammonium chloride there was a greater amount of calcium in the fæces than had been ingested. From these results it is justifiable to conclude that in ammonium-chloride acidosis excretion of calcium through the bowel wall can occur. Our results also contradict the statement of Givens and Mendel[20] that the increase in urinary calcium in acidosis is the result of diversion of lime from stools to urine. In our cases both the urinary and fæcal lime was increased in amount.

In one period at least (N.M., 2nd period) there was unequivocal evidence of calcium excretion by the bowel wall. Since, however, there was no alteration in the lumen of the gut other than the temporary presence of ammonium chloride which we shall show was practically completely absorbed, it seems reasonable to assume that absorption of lime was unaltered during the ammonium chloride period. The excess of fæcal calcium must therefore have been the result of excretion by the bowel wall. On similar grounds it would appear that the excess of fæcal phosphorus in the ammonium chloride period was the result, not of decreased absorption, but of increased excretion through the wall of the intestine.

The investigations of Nelson[21] on the mineral metabolism of patients suffering from diabetes and of epileptic subjects fed on ketogenic diets have shown that the kidneys are capable of excreting large amounts of lime. Indeed, more than half the total excretion of calcium may take place through the urinary system. In these cases there is also a slight increase in the fæcal output of lime. The presence of an acidosis, therefore, leads to an increased

excretion of lime both by urine and fæces. In our series, with the exception of N.M., the percentage of lime excreted by the urine is always increased during the ammonium chloride period. This would suggest that the amount of calcium excreted by the kidneys is to some extent dependent on the degree of acidosis. Additional support would at first glance seem to be lent to this view by the results of Shohl and Sato[22], and Bogert and Kirkpatrick[4]. The former found that the addition of sodium bicarbonate to the diet decreased the urinary output of CaO and P_2O_5, but increased their content in the fæces to such an extent that the retention of each was reduced. Bogert and Kirkpatrick record similar results with a base-forming diet. The addition of sodium bicarbonate to the diet brings in another factor, namely, a change in the reaction of the lumen of the gut. The decreased urinary output of calcium during administration of bicarbonate may be entirely due to the local effect of this salt in interfering with the absorption of lime by increasing the pH of the intestinal contents.

Freudenberg and György[6] have advanced the theory that the decreased retention of calcium in rickets is due to an acidosis of the tissues which interferes with the precipitation of calcium salts. If this view were correct one would expect the mode of excretion of lime and phosphorus to be similar to that found during ammonium chloride acidosis. Quite the reverse obtains, since the output of lime in the urine is markedly diminished, as is also the urinary phosphorus; and the very low retention of these minerals is caused entirely by the large fæcal content of CaO and P_2O_5. In other words, the partition of calcium and phosphorus in the excreta in rickets closely resembles that found in conditions tending to alkalosis rather than acidosis.

TABLE 6.

SHOWING INTAKE, OUTPUT AND RETENTION OF CHLORINE (C.CM. N/10 Cl).

Name	Period	Intake	Output		Retention	
			Urine	Fæces	Total	Per kgrm. per day
N.G.	Normal...	4133	3585	36	+512	+2·8
	NH_4Cl	10675	9518	40	+1117	+6·1
W.C.	Normal...	4133	3815	15	+303	+1·6
	NH_4Cl	10675	9853	17	+805	+4·3
J.F.	Normal...	2755	2829	—	—74	—0·6
	NH_4Cl	8365	7299	—	+1066	+8·8
	NH_4Cl	8365	7656	—	+709	+5·8
N.M.	Normal...	4018	3706	—	+312	+1·5
	NH_4Cl	10560	10040	—	+635	+3·0
	NH_4Cl ... ... (5 days)	7545	7678	—	—133	—0·9

Chlorine.—The excretion of chloride normally takes place through the urine and the sweat. The fæcal output is practically negligible. It was estimated in two of our cases, and as will be seen from the results in Table 6 the fæcal excretion of chloride was relatively minute both during the control and ammonium chloride periods.

During the control period there was a small retention of chlorine except in the case of J.F. where there was a very slight negative balance. While ammonium chloride was being administered the retention was increased in every case except during the second period of N.M., which was characterized by a slight negative balance.

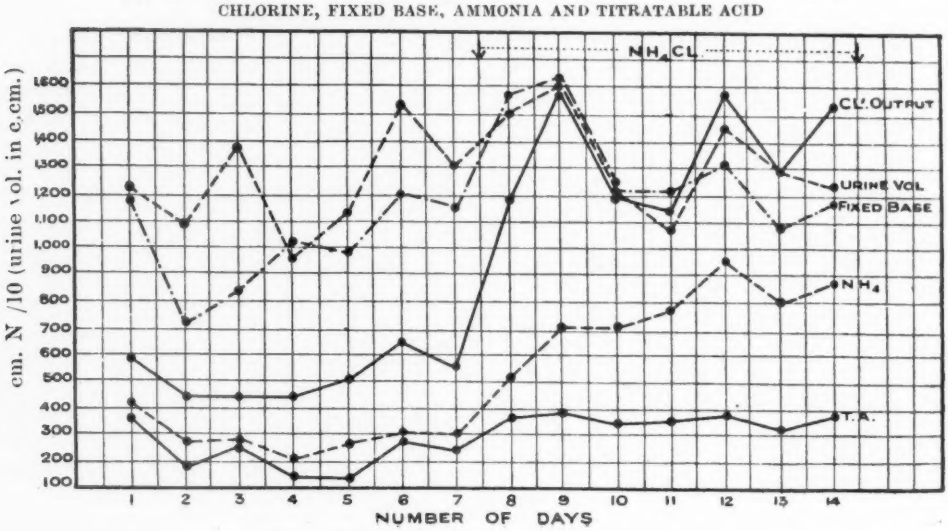
TABLE 7.

PERCENTAGE EXCRETION OF CHLORINE IN FIRST 24 HOURS FOLLOWING INGESTION OF SODIUM CHLORIDE.

Amt. of NaCl given	Form in which NaCl given	Diet	% Excretion of extra salt during 1st 24 hr.
4·5	Saline	Salt poor	53
4·5	Saline	Salt rich	62
10·0	Solid in capsule	Salt poor	50
10·0	Solid in capsule	Salt rich	67

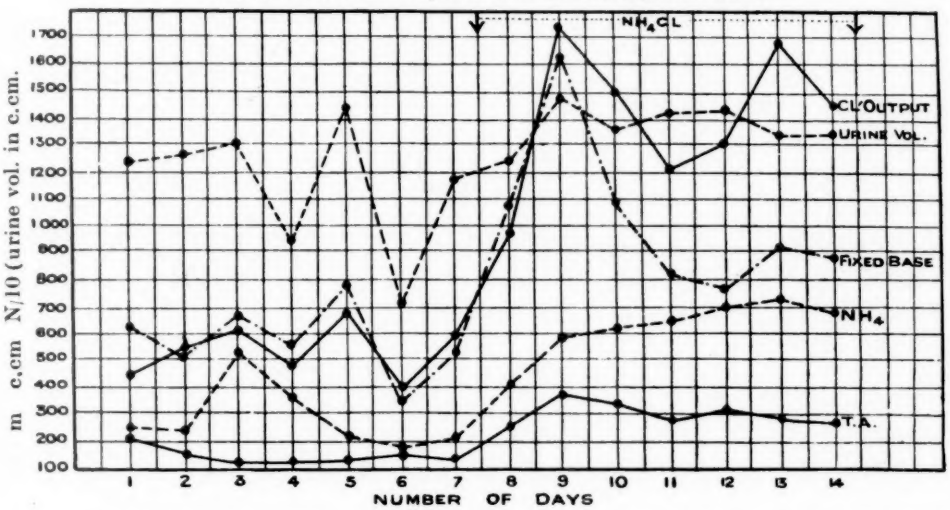
When one comes to examine the daily figures it is plain that all the subjects reacted immediately to the extra chlorine by the excretion of a greatly increased amount of this substance in the urine. In N.G. the output was doubled on the first day, so that only about 30 per cent. of the extra chlorine had been retained. This corresponds to what happens when sodium chloride is given. Table 7 indicates the percentage excretion of chlorine in the first 24 hours following ingestion of sodium chloride: the subject was a healthy boy aged 11 years.

FIG. 3. CASE N. G. GRAPH SHOWING DAILY URINARY OUTPUT OF WATER, CHLORINE, FIXED BASE, AMMONIA AND TITRATABLE ACID



With the exception of N.M. the daily curve of NaCl output (Fig. 3—6) during administration of ammonium chloride shows that the peak of chloride excretion occurred on the second or third day. This was followed by a drop lasting over two or three days, which was succeeded on the fifth or sixth day by a peak reaching almost to the level of the first. In the case of N.M. there was a complete absence of the first peak but the second was quite marked. It will be noted in every case that this second peak corresponded with the maximum rise in the output of ammonia. It is therefore fair to conclude that this secondary rise in the excretion of chlorine was due to the increased ability of the kidney to supply ammonia. Indeed, a glance at the chlorine and ammonia curves following this second peak shows in every case a fairly marked parallelism indicating a correlation between these two substances. This parallelism is not noticeable during the first five days of ammonium chloride administration. There is also a fairly marked correlation between the amount of urinary chloride and fixed base both during the control and the ammonium chloride periods, with the exception of the control period of N.G. The urinary volume and chlorides also show some parallelism especially during the ammonium chloride periods.

FIG. 4. CASE W. C. GRAPH SHOWING DAILY URINARY OUTPUT OF WATER, CHLORINE, FIXED BASE, AMMONIA AND TITRATABLE ACID.



Urinary volume.—Gamble, Ross and Tisdall[7] reported an increase of urinary volume in children during the administration of either calcium or ammonium chloride. Keith and Whelan[11], however, found no change in the volume of urine excreted by a normal individual during ingestion of ammonium chloride. During such administration there was in all our cases except the first period of N.M. an increase in urinary volume, not, however, as marked as might have been expected. The daily output of urine varied greatly, frequently falling much below the maximum observed in the control period.

Ammonia and titratable acidity of the urine.—The output of ammonia and titratable acid was increased in every case during the administration of ammonium chloride. The maximum output of titratable acid was reached

by the second day, following which there was usually a very gradual decline in the output. The ammonia content of the urine did not attain its greatest value till the 5th or 6th day, and in the case of J.F. the 9th day. Thereafter the output of ammonia remained at a constant level, except in the case of N.M. where considerable variations were observed from day to day. The ammonia output was not estimated in the days following the ammonium chloride period, but Gamble and others have shown that the output remains definitely above normal for some days following the administration of an acid salt.

TABLE 8.

SHOWING INTAKE, URINARY AND FÆCAL OUTPUTS AND RETENTION OF FIXED BASE (C.CM. N/10 MONOVALENT BASE).

Name	Period	Intake	Output			Retention	
			Urine	Fæces	Total	Total	Per kgrm. per day
N.G.	Normal ...	16254	7172	4561	11733	4521	24·5
	NH_4Cl ...	16254	9105	5397	14502	1752	9·4
W.C.	Normal ...	16254	5442	6579	12021	4233	22·4
	NH_4Cl ...	16254	8434	6695	15129	1125	6·0
J.F.	Normal ...	10836	4494	4135	8629	2207	18·1
	NH_4Cl ...	10836	5465	5036	9501	1335	11·0
	NH_4Cl ...	10836	5841	4069	9910	926	7·5
N.M.	Normal ...	15803	5726	5563	11289	4514	21·5
	NH_4Cl ...	15803	8229	8039	16268	—465	— 2·2
	NH_4Cl ...	11290	6616	7617	14233	—2943	—19·6

Fixed base.—The output of fixed base (Table 8) was with the exception of the control period of W.C., and the second ammonium chloride period of N.M., somewhat greater by the urine than by the fæces. The fæcal output of base was chiefly composed of calcium which constituted from 70 to 90 per cent. in the control periods and 77 to 99 per cent. in the ammonium chloride periods (Table 9). Thus, not only did ammonium chloride increase the output of fixed base by the fæces, but it also raised the proportion of calcium to other base. In the urine the calcium formed 5·4 to 11·1 per cent. of the fixed base in the control periods and 11 to 15 per cent. in the test periods. The urine, therefore, showed during administration of ammonium chloride an increase in total fixed base, and a slight rise in the relative proportion of calcium to other base. The urinary fixed base reached its maximum within three days of the commencement of administration, thereafter falling to slightly above the average level of the control period. This is in agreement with the findings of Gamble, Blackfan and Hamilton[8] with several acid-producing salts. The retention of fixed base varied from 18·1 to 24·5 c.cm. N/10 per kgrm. of body

TABLE 9.

SHOWING RELATIONSHIP OF OUTPUTS OF CALCIUM AND TOTAL FIXED BASE.

Name	Period	% of calcium to output of total fixed base	
		Urine	Fæces
N.G.	Normal	7·0	74·3
	NH_4Cl	11·5	82·4
W.C.	Normal	10·0	89·8
	NH_4Cl	11·0	99·0
J.F.	Normal	5·4	74·1
	NH_4Cl	14·0	79·0
	NH_4Cl	12·8	77·5
N.M.	Normal	11·1	70·1
	NH_4Cl	13·8	87·6
	NH_4Cl	15·0	83·3

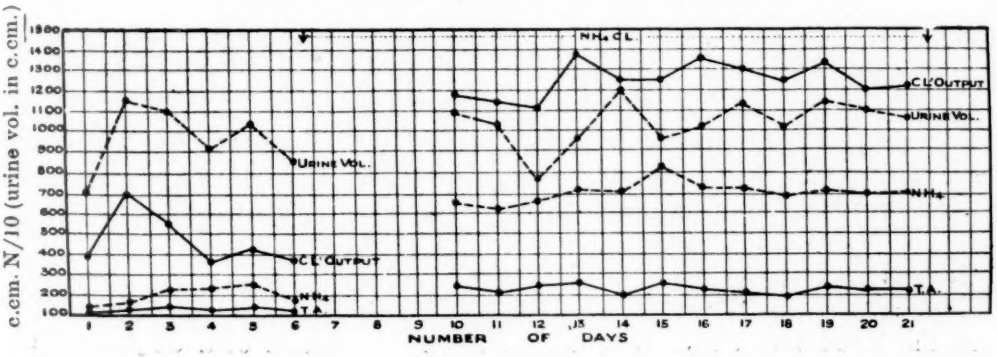
weight per day during the control periods. It was always diminished during ammonium chloride administration, and was negative during both the periods of N.M., the loss being entirely accounted for by calcium.

Metabolic reactions to acidosis.

Against the production of a non-gaseous acidosis such as is produced by ammonium chloride the organism has the following general defences :—(1) an increase in the available base of the blood ; (2) an increased excretion of volatile acid by the lungs ; and (3) an increased supply of base for neutralizing acids that are to be excreted.

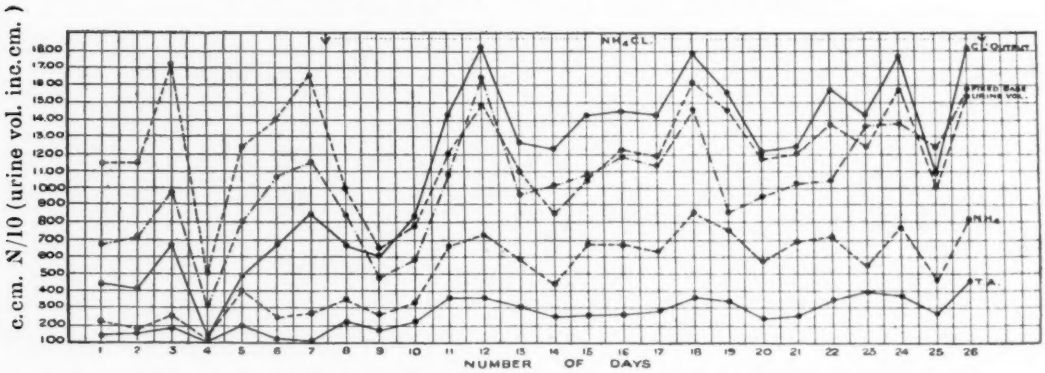
(1) **Increase in available base of the blood.**—The fixed base is maintained at a fairly constant level. By a reduction in the CO_2 content of the

FIG. 5. CASE J. F. GRAPH SHOWING DAILY URINARY OUTPUT OF WATER CHLORINE, FIXED BASE, AMMONIA AND TITRATABLE ACID.



blood a certain amount of base is freed and rendered available for the neutralization of other acid radicles. It has been shown that the base-combining powers of protein and inorganic phosphorus are reduced with a fall in the pH of the blood, but the amount of base released by these changes in such a condition as prevails in the experiments detai ed here is practically negligible. The fall in blood-CO_2, therefore, undoubtedly constitutes the chief immediate response to acidosis of the non-gaseous variety. In the subjects of this study the increase in available base produced by the reduction in CO_2 could not have amounted to more than 230 c.cm. N/10 (on the assumption that the blood-volume was one-thirteenth of the body weight). One gramme of ammonium chloride (i.e., one-fifth of the daily intake) contains 187 c.cm. N/10 acid. Two such doses are therefore much more than sufficient to use up all the base made available by the reduction in CO_2. The relief afforded by this means is only temporary, since prolonged administration of ammonium chloride does not to any extent further reduce the CO_2 content of the blood. The state of affairs produced in our subjects corresponds according to the nomenclature of Van Slyke to the condition of compensated acidosis (i.e., a fall in bicarbonate without symptoms of acidosis or change in the pH of the blood.) Although the pH was not actually estimated it is safe to assume that the absence of

FIG. 6. CASE N.M. GRAPH SHOWING DAILY OUTPUT OF WATER CHLORINE, FIXED BASE, AMMONIA, AND TITRATABLE ACID.



noticeable respiratory changes indicated an absence of any change in the pH of the blood that would be detected by physico-chemical means.

In clinical acidosis figures for total CO_2 have been noted much lower than the lowest in the present series. Such low figures supply definite evidence of an inability of the other compensatory mechanisms to deal with the situation either because of the suddenness of the demands (as in Haldane's case with an avalanche of 25 grm. of ammonium chloride), or because of the functional inefficiency, relative or absolute, of the other defensive reactions, as in diabetic or uræmic coma.

(2) **Increased excretion of volatile acids by the lungs.**—Respiratory changes leading to an increased output of CO_2 must naturally follow the displacement of CO_2 from its union with base. Otherwise the tension of CO_2 in the blood would increase and lead to the production of a CO_2 acidosis

(gaseous). In our cases, as would be expected from the results of the CO_2 analyses of the blood, there were no marked respiratory alterations. The excretion of the extra CO_2 must have been of such relatively small amount that no apparent strain was put on the respiratory system.

(3) **Supply of base for the excretion of acid.**—The kidney is undoubtedly the principal organ for the excretion of the non-volatile acid radicles. The sweat glands may play an important part in the metabolism of chlorine when large amounts of sweat are produced, although Schwenkenbecker and Spitta[24] conclude that not more than one gramme of sodium chloride is excreted daily even during profuse sweating. In the absence of hyperidrosis, at any rate, it is justifiable to assume that the amount of electrolyte lost in this way is practically negligible. The bowel certainly plays a part in mineral metabolism, but as far as the actual excretion of chlorine is concerned the intestinal output is negligible. Accordingly we may conclude that the extra acid supplied in these experiments must have been excreted by the kidneys.

At the lowest possible value of the urinary pH chlorine cannot be excreted as a free acid, requiring therefore a full equivalence of base. This base can be obtained in three ways. (a) Base may be released from weak acids which can be excreted either free or with only a partial complement of base. (b) Extra ammonia may be formed. (c) Fixed base may be supplied from the tissues and tissue-fluids.

(A) Release of base from weak acids.—This is, of course, an accompaniment, if not the result, of increased acidity of the urine, which decreases the base-combining powers of the weaker acids. Change of phosphate from the mono-hydrogen to the di-hydrogen variety forms the best example of the saving of base effected in this way.

If we assume that during the control period the pH of the urine was 6·81, and during the NH_4Cl period 5·91, the amount of base saved by change of phosphate from Na_2HPO_4 to NaH_2PO_4 may be calculated as follows :—

at pH 6·81—50 per cent. of phosphorus is in the form of NaH_2PO_4

" " 5·91 90 " " " " "

Of 1000 mgrm. phosphorus.

at pH 6·81 500 mgrm. are present as NaH_2PO_4

" " 5·91 900 " " " "

In changing, therefore, from pH 6·81 to pH 5·91, 400 mgrm. are converted from the mono-to the di-hydrogen variety. Since one H-ion is involved in the change of each phosphate molecule it would require 1 litre of normal acid to change 1 litre of normal phosphorus (i.e., 31 grm. phosphorus) from the mono-to the di-hydrogen phosphate.

To change 400 mgrm. P. would require $\frac{0{\cdot}400 \times 1000}{31}$ c.cm. N/1 acid, (i.e., 13 c.cm. N/10 acid).

By change of urinary pH from 6·81 to 5·91 there will be a saving of 130 c.cm. N/10 base per every gramme of phosphorus excreted.

This saving is indicated by the increase in titratable acidity. The response of the urinary system in this direction reaches its maximum within a very short time of the commencement of ammonium chloride administration. The base so released amounts, however, to only a small part of that likely to be required in any but the very mildest forms of increased acid excretion, and it certainly would be hopelessly inadequate to meet the requirements of even the smallest degree of acidosis that could be recognised clinically.

(B) INCREASE IN AMMONIA FORMATION.—The work of Benedict and Nash[25] has shown that ammonia is formed in the kidney. In cases of marked renal inefficiency the ammonia output is low: this must play an important part in the production of renal acidosis. In the subject with normal renal function the supply of ammonia forms a most important bulwark against acidosis. The increase in ammonia formation takes some time to reach its maximum. Some mechanism is therefore required to tide over the needs of the excretory system for more base until the supply of ammonia is sufficient to meet the demands. This mechanism will be discussed in the next section, but before leaving the question of increased ammonia production it is well to remember that the increase in ammonia output is continued after the need for increased acid excretion has ceased. As Gamble and his co-workers have pointed out this continued formation of ammonia is of vital importance in restoring the depleted stores of body base to normal.

(C) SUPPLY OF FIXED BASE FROM TISSUES AND TISSUE-FLUIDS.—This method provides the chief immediate means whereby excess anions are excreted. The base may be derived from the bones or from the other tissues in which latter case it must be accompanied by fluid in order to prevent disturbances of osmotic equilibrium.

In the bones calcium is found as phosphate with a small amount of carbonate. Accordingly the release of calcium entails the freeing of phosphorus which must also be excreted. In this transaction, however, there is a distinct saving of base. In bone two equivalents of phosphorus neutralize three equivalents of calcium (i.e., six equivalents of monovalent base). As excreted, however, the phosphorus in the urine is monovalent while in the fæces it has probably about the same valency as in the plasma, namely, 1·8. Accordingly for every equivalent of bone phosphorus excreted in the urine we have the saving of two equivalents of base, while for every equivalent in the fæces the saving effected is 1·2 (=3—1·8).

If it is assumed that the excess of calcium excreted is derived in proportionately equal amounts from the carbonate and phosphate of the bone, then one-fifth of this excess comes from the carbonate. Therefore the amount of base rendered available by the release of calcium carbonate may be calculated as the equivalents of monovalent base contained in one-fifth of the total excess calcium found in the excreta. The amount of base obtained from the phosphate may be calculated from the excess phosphorus as follows:—

(Excess urinary P. in c.cm. N/10 × 2) + (Excess fæcal P. in c.cm. N/10 × 1·2).

It may be objected that not all of the extra calcium and phosphorus come from bone. As the calcium content of the non-osseous tissues is relatively minute, bone must form the chief source of calcium. Phosphorus, however, plays an important part quantitatively in practically all metabolic processes. In three of our cases there was more extra phosphorus than extra calcium found in the excreta, thus showing that bone is not the source of all the extra phosphorus. The amount of extra phosphorus excreted from the extra-osseous source must form, however, only a small fraction of the total, and can only modify slightly the saving of base as calculated from the above formula.

The fixed base from the non-osseous tissues consists almost entirely of sodium and potassium, the former derived chiefly from extra-cellular, the latter being mainly an intra-cellular constituent. In either case, however, the base is associated with an equivalent amount of acid. If this base is excreted, some means must be found for dealing with its anions. Of these CO_2 is excreted by the lungs, while protein which holds about ten equivalents of base is probably katabolized. With the exception possibly of some of the organic acid, the remaining anions demand their full quota of base for neutralizing purposes. The water carrying the base must also be got rid of in order to prevent an upset of osmotic equilibrium. Accordingly for every 150 c.cm. N/10 base there will be rendered available only about 40 c.cm. N/10 for neutralizing extra acid. This 40 c.cm. is made up of 24 c.cm. from $B.HCO_3$ and the remainder from B. protein and organic salts. The efficiency in supplying base is thus only 26 per cent., even when blood plasma is the fluid called upon, and must be less in the case of the tissue-juices where the protein content is lower. Accompanying this 150 c.cm. N/10 base will be 100 c.cm. water which will contain its normal quota of fixed acid (Cl',SO''_4). The amount of tissue fluid excreted during the ammonium chloride period is indicated by the increase in urinary volume. The chlorine content of this excess in urinary volume should, if the hypothesis put forward be correct, approximate to that of the plasma.

TABLE 10.

SHOWING THE MEANS EMPLOYED IN NEUTRALISING THE EXCESS ACID.

Name	(1) Incr. in Cl′	(2) Incr. in T.A.	(3) Incr. in NH_4	(4) Incr. base derived from $CaCO_3$	(5) Incr. base derived from Fæcal P′	(6) Incr. base derived from Urinary P′	(7) Tissue fluid base	(8) Incr. in urinary volume	(9) Calculated c.cm. N/10 B.Cl per 100 c.cm. excess H_2O
N.G.	5933	917	3298	320	370	192	837	850	98·4
W.C.	6038	1172	2452	145	30	896	1343	1475	91·1
J.F.	4470	527	3051	285	355	36	216	231	93·5
	4827	503	3670	116	40	nil	498	526	94·7
N.M.	6334	1150	2768	721	1340	236	121*	nil	—

*This amount of fixed base was probably supplied without the accompaniment of fluid by the reduction of the fixed base content of the blood by 15 c.cm. N/10 per 100 c.cm.

In Table 10 are given the figures indicating the methods whereby the excess of excreted acid (chlorine) has been neutralized. Column 1 gives the values for the excess excretion of chlorine. Columns 2 to 7 indicate the amount of base derived from the sources indicated for the neutralization of this excess chlorine. The figures in columns 2 to 6 are calculated from the

results of the analyses, but those in column 7 have been obtained as follows :— Cl—(T.A. $+NH_4+$Base derived from bone). Our results do not contain values for sulphates and organic acids which, as has been shown by Gamble, are also excreted in excess during acidosis. These acid radicles probably come from tissue juices and carry down with them their quota of base from the tissue-juices. Thus by calculating the figures in column 7 in the manner stated, we obviate any error due to the presence of excess sulphates. The base figures given in column 7 indicate the amount of tissue-fluid base combined with chlorine, in other words the amounts of B.Cl. Accordingly if these figures are divided by the corresponding increase in urinary volume (column 8) the results obtained should give the value for the percentage of B.Cl. in the tissue fluid (column 9). It is evident that these values lie between 90 and 100, therefore within the normal limits of chlorine in plasma and presumably in tissue juice. Despite the fact that the method of calculation is and must be one of comparatively rough averages, we feel that the consistency of the values so obtained is sufficiently striking to afford strong support to the thesis which has been advanced.

Several further points may be noted. If the view proposed is correct, one would have expected that the bulk of the excess phosphorus would have been excreted in the urine, since output by the kidneys effects a saving of two equivalents of base per equivalent of phosphorus, whereas for fæcal excretion the economy achieved is only 1·2. The fact that the bulk of the excess phosphorus is not excreted in the urine is probably related to the fact that there is a close association between the calcium and phosphorus in the fæces.

Administration of hydrochloric acid has been shown to increase the urinary output of phosphorus. This has been attributed to a change of reaction in the intestinal lumen producing a better absorption of phosphorus. In the light of our results, which also show an increased fæcal excretion, it would seem reasonable to refer both the increased urinary and fæcal excretion to the necessity for providing more base in the manner indicated.

Another point of interest is the different extent to which the various mechanisms are brought into play in reacting to excess acid. For the immediate supply of base both bone and tissue-juices are called upon. The one exception to this is the ammonium chloride period of N.M., where practically all the necessary fixed base was derived from bone ; less urine was passed than in the control period indicating a lack of response on the part of the tissue fluids. As to the rapidity with which the osseous tissue responds to the stimulus of an acidosis we have no data. H. L. White[26] obtained an increased urinary output of phosphorus within four hours of the administration of acid, but considered this merely a temporary phenomenon. Haldane, Hill and Luck[27], however, found a definite increase in the urinary output of phosphorus for 24 hours following the ingestion of large amounts of $CaCl_2$. On the other hand Gamble, Blackfan and Hamilton[8] observed no significant change in phosphorus excretion after the intake of moderately large amounts of acid.

Summary.

1. The effect of prolonged administration of ammonium chloride on the metabolism was studied in four apparently normal children, in none of whom was produced any clinical manifestation of acidosis.

2. Chemical changes in blood. (a). The CO_2 was reduced ; the reduction almost always reached its maximum early in the administration of ammonium chloride.

(b). The chlorine was moderately increased. The increase in chlorine did not exactly balance the deficiency in CO_2.

(c). The fixed base remained within normal limits except in one case where it was reduced by 15 milli-equivalents.

(d). The calcium was slightly increased and the phosphorus slightly diminished.

(e). The non-protein nitrogen was slightly increased but within normal limits.

3. Metabolism. (a). There was an increased output of calcium both by urine and fæces and consequently a decreased retention. Evidence is adduced in favour of the excretion of calcium through the bowel wall.

(b). There was an increased excretion of phosphorus by urine and fæces and a diminished retention.

(c). There was a slightly increased retention of chlorine. There were usually two peaks in the excretion of chloride : they occurred about the second and sixth days. The second peak usually coincided with the maximum output of ammonia.

(d). There was an increased excretion of fixed base both by urine and fæces. The extra fæcal base consisted chiefly of calcium.

4. The metabolic reactions to acidosis are discussed, and it is suggested that the increase in the output of calcium and phosphorus is the result of the response of the osseous tissues and forms a reaction of prime importance in the defence of the organism to acidosis. Evidence is brought forward from the result of the study in support of this thesis.

We desire to express our thanks to the Medical Research Council for assistance in this work, and for a personal grant to one of us (N.M.).

Analytical methods used :—Total CO_2—Haldane : Chlorine—Whitehorn : Non-protein nitrogen—Folin and Wu : Fixed base—Stadie and Ross : Calcium—Kramer and Tisdall : Phosphorus—Tisdall : Titratable acidity of urine—using phenolphthalein as indicator.

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A CASE OF EXOPHTHALMIC GOITRE

BY

FRANCES BRAID, M.D., M.R.C.P.,
Physician, Children's Hospital, Birmingham ;

and

A. V. NEALE, M.D., M.R.C.P.,
Physician to Out-Patients and Pathologist, Children's Hosp., Birmingham.

There are so few records of cases of exophthalmic goitre in children under the age of five, that it seems worth while to report this fatal case. The literature on the subject has been reviewed recently by Helmholz[1] and McGraw[2].

Case report.

LILIAN L., aged 2½ years, was seen at the Children's Hospital, Birmingham, in May, 1928.

The maternal grandmother had a small adenoma, the size of a walnut, of the thyroid gland. The mother, aged 27, had had an uniformly enlarged thyroid gland 'for as long as she could remember.' There were no associated symptoms. The father was healthy, but he had one brother who had a simple goitre at age of 16.

Fig. 1. On admission at 2½ years.

Patient was the first child. During her pregnancy the mother was in bed nearly all the time because of vomiting. The child was suckled for 11 months, and all was well till age one year, when she had double pneumonia and was very ill for three weeks. After that she became very nervous. The enlargement of the neck was noticed for several weeks, and the bulging of the eyes for two weeks before seeking advice.

The appearance of the child at this time is shown in Fig.1. Her nutrition was good and skin moist. Her weight was 1 stone 9 lb. The thyroid gland was uniformly enlarged and soft, and pulsated. There was appreciable exophthalmos: no tremor. The deep reflexes were brisk,

The area of cardiac dullness was somewhat increased, and there was marked tachycardia. While under observation for 10 days the rate varied from 110–150. The heart sounds were closed. The tonsils were much enlarged, but did not look unhealthy.

Blood examination showed a high leucocytosis. This can be explained by the fact that the child happened to be in the incubation stage of measles, the rash of which, along with Koplik spots, appeared on the tenth day after admission to hospital.

The resting blood sugar was 72 mgrm. One hour after the administration of 20 grm. of glucose it had risen to 403 mgrm. and 2 hours after had fallen to 141 mgrm. The urine contained ·12 per cent. sugar.

COURSE.—She was not seen again until August. All the features of the disease were now more marked, and her appearance is shown in Fig. 2. From May to August she had gained 1 lb. in weight. She was much more excitable, and had become unmanageable at home.

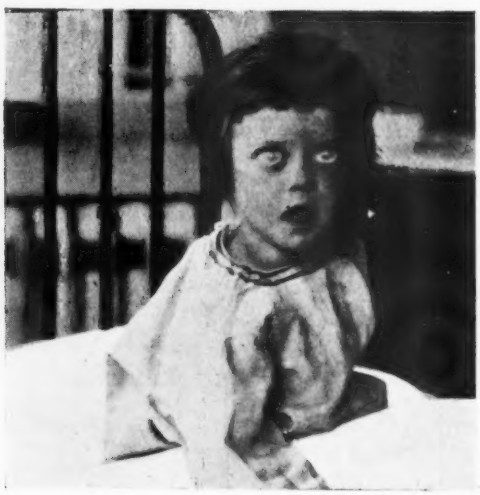

Fig. 2. Condition three months later.

Exophthalmos was more pronounced. The thyroid gland appeared to be larger. The heart enlargement is shown in the X-ray photograph (Fig. 3). Tachycardia was more pronounced, and the rate varied from 120–170. A systolic murmur was now audible. The thymus gland was markedly enlarged, as is shown by X-ray. The tonsils were still enlarged and congested.

Blood examination showed a lymphocytosis :—red cells, 5,680,000 ; white cells, 16,200 ; (polymorphonuclears 23 per cent., small lymphocytes 65 per cent., large lymphocytes 12 per cent.).

Sugar tolerance was not re-tested and sugar was not again detected in the urine. An attempt to estimate the metabolic rate was not successful. Tremors were not present.

TREATMENT.—During a period of five weeks, under medical treatment, the child lost weight, and the tachycardia persisted. Administration of iodine had no effect.

Operation for removal of the right lobe of the thyroid was undertaken by Mr. Lloyd on September 14th, under general anæsthesia. She appeared to stand the proceedings very well when, almost at the point of completion of the operation, she expired suddenly, presumably from heart failure.

AUTOPSY.—A well nourished child. The right lobe of the thyroid gland had been removed but the remaining portion was uniformly enlarged. The site of operation was free from hæmorrhage. The air passages were free from obstruction. The most prominent organ seen on opening the thorax was a greatly enlarged thymus gland, overlapping the heart, great vessels

and lungs to a remarkable extent. The thymus weighed 96 grm. (The normal weight of the gland for this age is 20 grm.) The lungs showed some area of collapse, possibly due to the pressure of the enlarged thymus. The heart appeared to be somewhat hypertrophied.

The lymphoid tissue throughout the body showed well marked general hyperplasia, this being specially seen in the small and large intestines, the spleen, the pharynx and the cervical and mesenteric glands. The liver, kidneys and brain were normal.

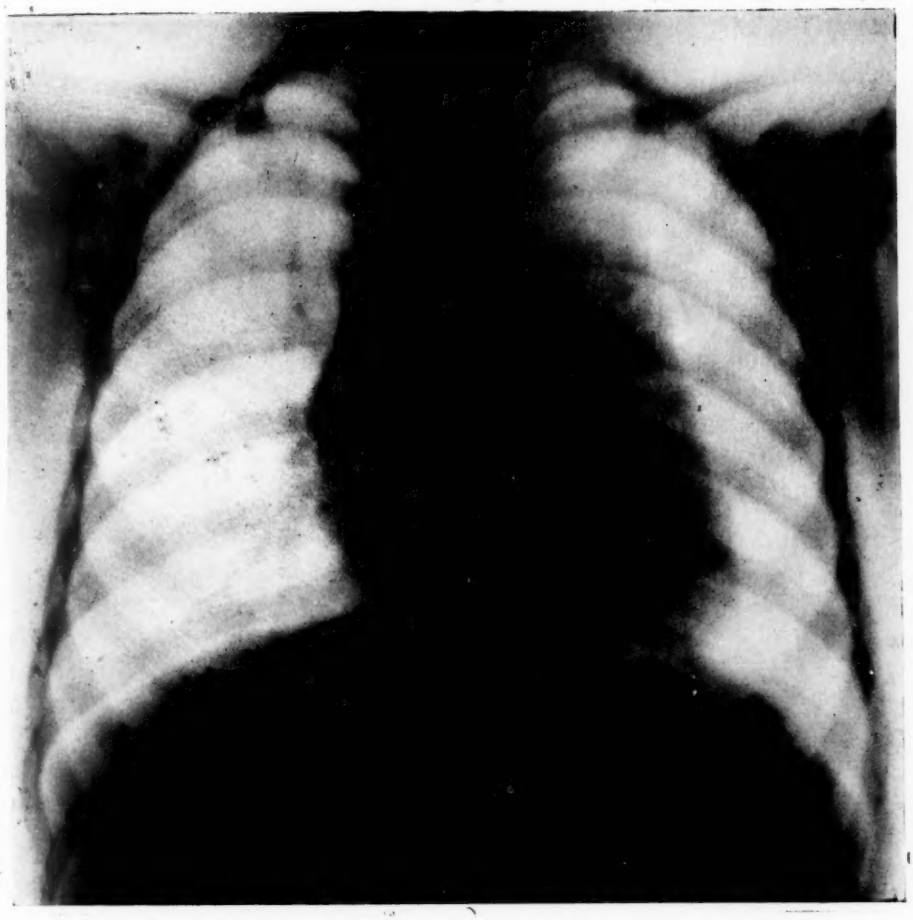

Fig. 3. Skiagram showing enlargement of heart and thymus.

HISTOLOGICAL EXAMINATION.—The thyroid gland showed a marked hyperplasia of the alveolar epithelium. Several areas showed papilliferous extensions of the secretory epithelial cells, thus greatly increasing the surface area of the secreting tissue. The vascularity was pronounced throughout. There was no evidence of inflammatory or neoplastic change (Fig. 4).

The thymus gland showed a well marked lymphoid hyperplasia and some increase in the smaller blood vessels. Hassal's corpuscles were present in very large numbers and distributed fairly regularly throughout the gland. The pituitary gland appeared normal. The cells of the anterior lobe showed well marked granular eosinophilic and basophilic staining. The cortical substance of the supra-renal glands was well differentiated and stained normally. The cells in the medulla were healthy and the blood spaces intact.

The cardiac muscle stained well and showed no degenerative signs. In some areas small collections of mononuclear leucocytes occurred. The blood vessels were healthy. The lymph glands and spleen showed simple hyperplasia.

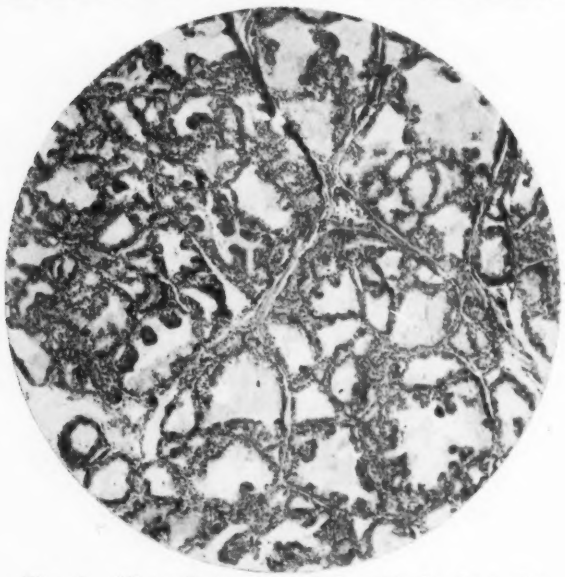

Fig. 4. Microphotograph of thyroid gland (× 40).

The case illustrates the importance of thyroid disorder in the mother in producing thyroid instability in the child, and suggests its responsibility for the status thymo-lymphaticus which here is more likely to be congenitalthan secondary to the increased blood supply to the gland.

Infection was the exciting factor, and the first acute respiratory infection, at the age of twelve months, was followed by signs of hyperthyroidism. Intercurrent infection rendered the condition more acute.

The clinical picture did not differ in essentials from that in an adult, with the notable exception that tremors were never present. This seems to be a fairly constant finding in children. The first symptom was nervousness, and was present for more than twelve months before the parents sought advice. Helmholz has drawn attention to this long initial period in which the true nature of the illness is not recognized. That being so, and ' nervousness ' being an early complaint in exophthalmic goitre, it would appear to be a symptom demanding more than cursory attention in the child of a goitrous mother.

The prognosis in older children appears to be reasonably good, but there are on record only two cases of recovery in children under the age of five years. Dreschfeld's[3] case, a girl aged three years, who had persistent diarrhœa, recovered after treatment with belladonna and pancreatic emulsion, and was well at the age of seven years. It is difficult to estimate the severity of the case. Helmholz reported a case of recovery after thyroidectomy in a child aged three years. The case now recorded was considered a good surgical risk, and apparent failure of the usual medical treatment seemed to justify operation. The pathological findings were similar to those in the adult, with the exception of the very marked enlargement of the thymus.

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A RIGHT-SIDED TRUE DIAPHRAGMATIC HERNIA WITH UNUSUAL FEATURES

BY

GLADYS H. DODDS, M.D., D.P.H.,

and

J. A. POCOCK, L.R.C.P., M.R.C.S.

(From the Obstetric Unit, University College Hospital, London.)

Congenital diaphragmatic hernia is a rare and grave condition. It is well known as a cause of still-birth and neonatal death. Of 127 cases reviewed by J. S. Latta[1] the age was given in 112 cases and of these 88 were either still-born or died within a few hours of birth. In a series of 57 cases collected by Funck Brentano[2] 51 cases were either still-born or died within 24 hours of birth.

The term diaphragmatic hernia is applied to any protrusion of the abdominal contents through the diaphragm. In a majority of the cases the abdominal contents pass through an opening in the diaphragm not constituting a hernia in the true sense of the word but a spurious diaphragmatic hernia. The true diaphragmatic hernia projects into the pleural cavity through a space in the muscle covered by peritoneum and pleura. Among 80 cases of congenital hernia collected by Bohn[3] a hernial sac was present in only 14. The left side is more frequently affected than the right. Of 42 cases of diaphragmatic hernia according to Popp[4], 37 were on the left side and only 5 on the right. Of Latta's 127 cases only 17 were on the right side. Further, when the right side is affected the hernia is usually small. Spencer[5] records two cases of large right-sided diaphragmatic herniæ. According to Ballantyne[6] the male sex seems to be more liable to diaphragmatic hernia than the female; thus in 67 case records examined by him 47 were males and 20 females. Only occasionally is the diaphragmatic defect accompanied by other developmental defects, except that of an undeveloped lung, and in practically all cases the child is normal in external appearance.

The following case is recorded not only on account of the rarity of the large right-sided true diaphragmatic hernia, but also because of the associated mal-development of suprarenal gland and secondary herniation of the primary sac.

Case report.

Baby B., female, was born on the district of the Obstetric Hospital, University College Hospital, a few minutes before the arrival of the attendants. The baby was blue, cried feebly and gasped about four times to the minute. It lived for nearly half an hour. The mother was a healthy woman aged 33 years. Her Wassermann reaction was negative. She had had 6 previous children, all of whom were alive and healthy and showed no deformity.

POST-MORTEM EXAMINATION.—Full-time, female child, weight 3,200 grm., length 49 cm. Externally the child showed no deformity. On opening the thoracic cavity a large solid structure similar in appearance to the liver was noted lying within a sac in the right pleural cavity. On opening the sac this lobe of liver was found to occupy the entire anterior part of the right side of the thorax. It corresponded in shape to the thorax, the inner left margin was almost vertical and reached an apex at the level of the 3rd rib, where the right margin sloped outwards towards the ribs. On the postero-lateral surface of this lobe of the liver the gall-bladder was recognized, attached closely to the liver. The apex of the gall-bladder reached the antero-lateral margin of the liver at the level of the 4th rib in the mid-axillary line. The gall-bladder lay in an almost vertical plane, hence the neck of the gall-bladder was close to the opening in the diaphragm. Posterior to the liver lay intestines. The right lung was undeveloped but showed normal lobulation, and lay against the thoracic vertebræ posterior to the hernial sac. The heart was pushed over into the left thorax, but was otherwise normal. The left lung was small and undilated, but normal in shape and fissuring. The thymus was small, weighing 2 grm.

On opening the abdominal cavity the liver and large intestine presented. The abdominal liver had a right and a left lobe. The left lobe was the larger of the two and was normal in shape. The right lobe was almost square and was about half the size of the left lobe. On the inferior surface of the right lobe a caudate lobe of normal size was seen in its normal position, but quadrate lobe, portal tract and gall-bladder were absent. The gastro-hepatic omentum extended from the depression on the liver anterior to caudate lobe on to the lesser curvature of the stomach. The stomach was normal in size and position. On raising the abdominal portion of the liver an aperture which admitted 3 fingers was seen in the antero-lateral aspect of the right side of the diaphragm. A sac consisting of peritoneum and pleura extended into the thorax from the margins of the hernial opening. A narrow neck of liver joining the abdominal and thoracic portions lay in the anterior part of the hernial opening; posteriorly were intestines.

The pylorus lay on the right side of the first lumbar vertebra and from it the first part of the duodenum passed upwards posteriorly and slightly to the left into the thorax, where it lay in close proximity to the neck of the gall-bladder. The second part of the duodenum curved laterally from the neck of the gall-bladder. The third part of the duodenum passed almost directly caudally into the abdominal cavity where it lay in direct contact with the posterior abdominal wall in the plane of right mid-axillary line. The head of the pancreas lay in the curvature of the duodenum. The second part of the duodenum was free, i.e., it was covered by peritoneum on all surfaces except where the head of the pancreas lay in contact with it. The common bile duct and pancreatic duct entered the second part of the duodenum.

The jejunum arose from the duodenum in the abdomen and passed immediately into the thoracic cavity posterior to the lobe of the liver. The small intestine filled the posterior area of the hernial sac. There was a secondary hernial sac, situated on the lower postero-medial aspect of the primary hernial sac, and this projected medially into the posterior mediastinum. The lower end of ileum, cæcum and appendix were found in this secondary hernial sac. The mesentery of the small intestine was attached to the posterior abdominal wall inferior to the posterior margin of the hernial opening; thus it was slightly superior and more lateral than normal. The ascending colon passed laterally from the posterior mediastinum into the abdominal cavity and became the transverse colon close to the pylorus. The ascending colon had a mesentery which was attached to the greater curvature of the stomach. The transverse, descending and pelvic colons were normal. Both kidneys, spleen and left suprarenal were normally situated. The right suprarenal was very small in size, and in weight was less than 1 grm. Microscopical examination of it revealed normal structure. The head of the pancreas was in the duodenal curvature in the thoracic cavity but the body and tail were normally situated in the abdomen, in relation to the stomach and spleen. There was no cerebral nor osseous deformity.

Discussion.

The development of the diaphragm is a complicated process. It is built up of 5 separate parts—one central, two ventro-lateral and two dorsi-lateral. At about the 6th week of embryonic life after the heart, lungs, liver and stomach

are in their permanent positions, the openings between the pleural and peritoneal cavities close and about the same time muscle fibres are laid down in the membranes which are forming the diaphragm. The true congenital diaphragmatic hernias are due to an abnormal development of the diaphragmatic muscle and any process which retards or prevents this may easily lead to a herniation at the point of defect. Why the muscle fails at times to develop is not certain. It may be a question of local pathology—some interference in circulation or some fault in innervation. In this case the phrenic nerves were present on each side, the left innervating the left side of the diaphragm and the right being distributed to the hernial sac on the right side.

Summary.

This case shows a combination of rare features :—(1) a large right-sided true diaphragmatic hernia in a female ; (2) abnormal fissuring of the liver and situation of the gall-bladder ; (3) the duodenum entirely confined to the right side of the body and not closely attached to the posterior abdominal wall ; (4) a mesentery attached to the ascending colon ; (5) a secondary herniation of the primary sac ; (6) a rudimentary suprarenal gland.

We are indebted to Professor F. J. Browne, Director of the Obstetric Unit, University College Hospital, for permission to publish this case.

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